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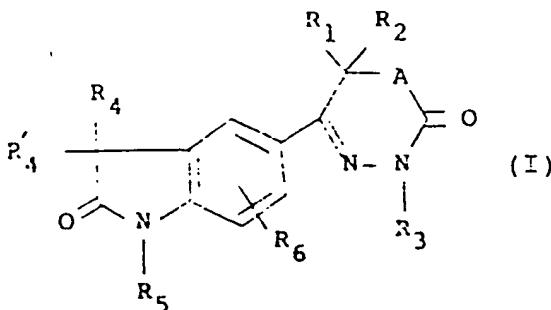
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Claims for the following Contracting State: ES.

The title of the invention has been amended (Guidelines for Examination in the EPO, A-III, 7.3).

(54) 2-Indolones substituted in 5 by a cyclic hydrazide radical, their preparation and their use in cardio-active medicaments.

(57) A compound of formula (I) or a pharmaceutically acceptable salt thereof,



arylcarbonyl, aryloxycarbonyl, lower alkoxy, lower alkoxy carbonyl, lower alkoxy carbonyl alkoxy, lower -thioalkoxy, hydroxy, nitrile, heterocycl, or -NRcRd, where Rc is hydrogen, lower alkyl, cycloalkyl, aryl, aralkyl, lower alkylcarbonyl, arylcarbonyl, aminocarbonyl, aminothiocarbonyl, aminoiminocarbonyl, lower alkoxy carbonyl, lower alkoxythiocarbonyl, aryloxycarbonyl, thiocarbonyl, nitrile, carboxy, heterocycl or heterocyclic carbonyl, and Rd is hydrogen or lower alkyl; Rb is hydrogen, lower alkyl, aryl, lower alkylcarbonyl, lower alkoxy carbonyl, nitrile or nitro; or R4 is -NH-Ra, in which Ra is as defined above, and R4' is hydrogen or lower alkyl;
each of R3 and R5 is independently hydrogen, lower alkyl, aryl, lower alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclic carbonyl, optionally substituted aminocarbonyl, lower alkoxy carbonyl or aryloxycarbonyl;
Rb is hydrogen, lower alkyl or halogen;
and A is sulphur, oxygen, -NH- or -CH₂-.

is useful for the treatment of heart disease.

in which,

R1 is hydrogen or lower alkyl;

R2 is hydrogen or lower alkyl;

R4 and Ra together form a group =N-Ra, or =CRaRb, where Ra is hydrogen, lower alkyl, aryl, aryloxy, lower alkylcarbonyl,

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Description

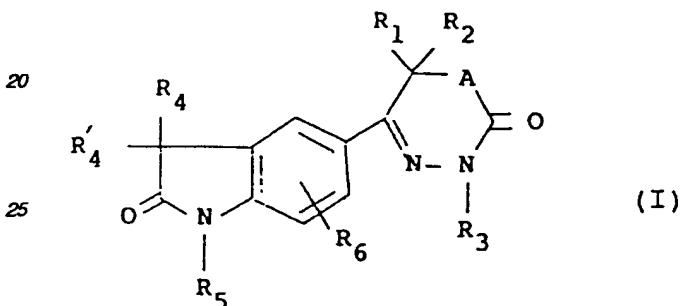
COMPOUNDS

This invention relates to compounds having pharmacological activity, pharmaceutical compositions containing them, processes for their preparation, and their use as active therapeutic agents, particularly in the treatment of acute or chronic heart disease.

EP-A-0052442 discloses phenyl-thiadiazinone, oxadiazinone or triazinone derivatives which are phosphodiesterase inhibitors and are said to possess cardiotonic properties. There is no disclosure in this document of the derivatives having the property of increasing the sensitivity of myocardial contractile proteins to calcium, which is believed to be an additional, useful mechanism of action for cardiotonic agents.

It has now been discovered that certain novel phenyl-thiadiazinone oxadiazinone and triazinone derivatives in which the phenyl nucleus forms part of a substituted 2-oxo-2,3-dihydroindole ring are phosphodiesterase inhibitors, and some of these derivatives may also increase the sensitivity of myocardial contractile proteins to calcium. The novel derivatives are therefore potentially valuable drugs in the treatment of congestive heart failure.

According to the present invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof:



in which,

R₁ is hydrogen or lower alkyl;

R₂ is hydrogen or lower alkyl;

R₄ and R_{4'} together form a group =N-Ra, or =CRaRb, where Ra is hydrogen, lower alkyl, aryl, aryloxy, lower alkylcarbonyl, arylcarbonyl, aryloxycarbonyl, lower alkoxy, lower alkoxy carbonyl, lower alkoxy carbonyl alkoxy, lower thioalkoxy, hydroxy, nitrile, heterocycl, or -NRcRd, where Rc is hydrogen, lower alkyl, cycloalkyl, aryl, aralkyl, lower alkylcarbonyl, arylcarbonyl, aminocarbonyl, aminothiocarbonyl, aminoiminocarbonyl, lower alkoxy carbonyl, lower alkoxythiocarbonyl, aryloxycarbonyl, thiocarbonyl, nitrile, carboxyl, heterocycl or heterocyclcarbonyl, and Rd is hydrogen or lower alkyl; Rb is hydrogen, lower alkyl, aryl, lower alkylcarbonyl, lower alkoxy carbonyl, nitrile or nitro;

or R₄ is -NH-Ra, in which Ra is as defined above, and R_{4'} is hydrogen or lower alkyl;

Each of R₃ and R₅ is independently hydrogen, lower alkyl, aryl, lower alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclcarbonyl, optionally substituted aminocarbonyl, lower alkoxy carbonyl or aryloxy carbonyl;

R₆ is hydrogen, lower alkyl or halogen;
and A is sulphur, oxygen, -NH- or -CH₂-.

The terms 'lower alkyl' and 'lower alkoxy' are used herein to mean straight or branched chain alkyl and alkoxy groups having up to 6, preferably up to 4, carbon atoms.

The term 'cycloalkyl' is used herein to mean a single optionally substituted ring having up to 12 carbon atoms in the ring.

The term 'aryl' is used herein to include optionally substituted carbocyclic aromatic groups, preferably having single or fused rings with 6 to 12 ring carbon atoms. Examples are phenyl and substituted phenyl. Examples of substituents are one or more atoms or moieties selected from amino, nitro, hydroxyl, lower alkyl, lower alkoxy, halogen, trifluoromethyl, lower alkyl sulphonyl and carboxyl, and they may be located in any position on the aromatic ring system.

The term 'aralkyl' is used herein to include aryl groups, as defined above, linked to an alkylene group which suitably contains from 1 to 6 carbon atoms. The alkylene group may itself be optionally substituted by, for example, a further aryl group. Examples are benzyl and substituted benzyl.

The term 'heterocycl' is used herein to include optionally substituted single or fused ring systems having 5 to 12 ring atoms, and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur. The ring system may be aromatic or non aromatic, and examples are pyridyl, thiényl or imidazolyl.

In a preferred group of compounds of formula (I), each of R₁, R₂, R₃, R₅ and R₆ is independently hydrogen or lower alkyl, particularly methyl, and A represents sulphur.

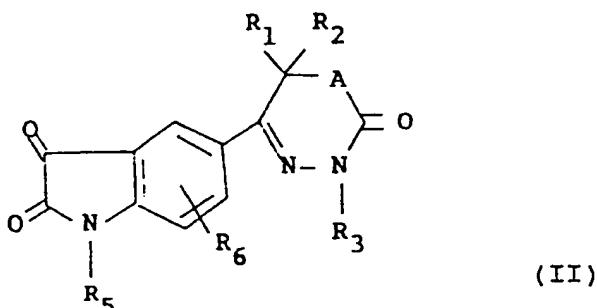
The compounds of the invention have two potential chiral centres at the R₄/R_{4'} and R₁/R₂ substituted positions, and can therefore exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including all enantiomers, diastereomers, and racemates.

The pharmaceutically acceptable salts of the compounds of formula (I), (when the compound contains a substitutable group) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α -keto-glutaric, α -glycerophosphoric, and glucose-1-phosphoric acids. Preferably the acid addition salt is a hydrochloride.

The compounds of the formula (I) and their pharmaceutically acceptable salts may also form solvates with pharmaceutically acceptable solvents, and such solvates are included within the expression 'a compound of formula (I)' used herein.

Salts of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts of compounds of the formula (I) or the compounds of the formula (I) themselves, and as such form an aspect of the present invention.

According to a further aspect of the invention, the compounds of formula (I) may be prepared by treating a compound of formula (II)



in which R₁, R₂, R₃, R₅, R₆ and A are as defined in formula (I) and W represents

$-\text{CH}_2-$ or $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$:

(a) when W represents

$-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$, with a compound of formula (III)



in which R₄R_{4'} represents $>\text{N}-\text{R}_a$, $>\text{CHR}_a$ or $>\text{CR}_a\text{R}_b$ as defined in claim 1, or

(b) when W represents $-\text{CH}_2-$, with a compound of formula (IV)

where R₄ and R_{4'} are $=\text{N}-\text{R}_a$ or $=\text{CR}_a\text{R}_b$ as defined in formula (I),

or with a diazonium salt containing an anion of formula (V)

$(\text{N}=\text{N}-\text{Rc})^+$ (V)

where Rc is as defined in formula (I),

and thereafter if desired converting a compound of formula (I) thereby produced to a pharmaceutically acceptable salt thereof or to a further compound of formula (I).

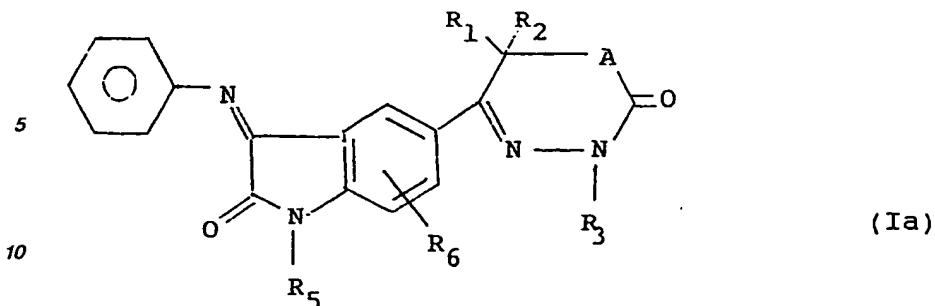
The reaction is preferably carried out in an organic solvent, for example ethanol, and in the presence of a base, such as potassium carbonate or sodium hydroxide. The reaction preferably occurs at between room temperature and the boiling point of the solvent, and for a period of from about 15 minutes to 3 hours.

The compounds of formula (I) may be converted into pharmaceutically acceptable salts in conventional manner by, for example, treatment with an appropriate acid.

Certain compounds of formula (I) may be converted to other compounds of formula (I) in accordance with known methods. For example, compounds of formula (I) in which R₄ and R_{4'} together represent $=\text{N}-\text{R}_a$ may be converted to compounds in which R₄ is $-\text{NH}-\text{R}_a$ and R_{4'} is hydrogen by reduction using zinc in acetic acid.

Generally speaking, it has been found that the latter compounds tend to be unstable, reverting to the unsaturated starting materials in the presence of air. However, the compounds can usually be stabilised by converting them to a salt form.

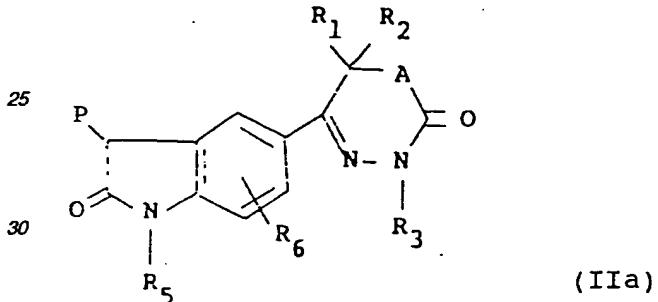
A particularly preferred, and novel, process for converting a compound of formula (I) to another compound of formula (I) comprises treating a compound of formula (Ia)



15 in which R₁, R₂, R₃, R₅, R₆ and A are as defined in formula (I), with a compound of formula (Va)
Ra-NH₂ (Va)

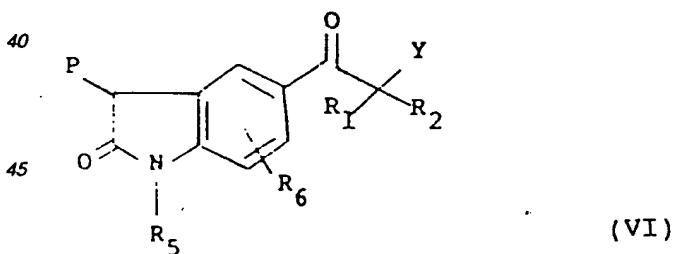
in which Ra is as defined in formula (I),
 to form a compound of formula (I) in which R4 and R4' are together the group =N-Ra.
 The compounds of formula (II) in which W is

20 -^{II}C- may themselves be prepared by oxidising a compound of formula (IIa)



35 in which R₁, R₂, R₅, R₆ and A are as defined in formula (I) and P is an oxidisable protecting group, such as thioalkyl particularly thiomethyl.

The compounds of formula (IIa) in which A is sulphur may themselves be prepared by treating a compound of formula (VI)



50 in which R_1 , R_2 , R_5 and R_6 are as defined in formula (I), P is as defined in formula (IIa), and Y is a leaving group,
with a compound of formula (VII)

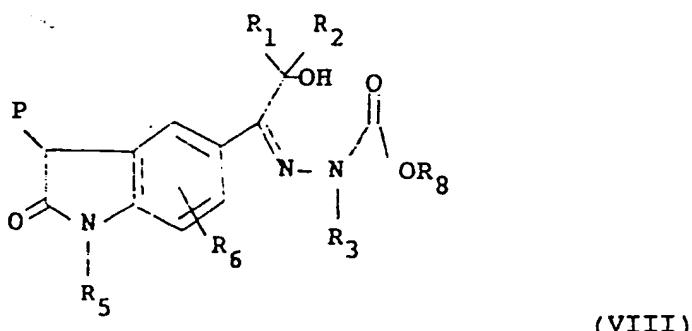


in which R₃ is as defined in formula (I), and Z is an alkyl group, preferably C₁₋₆ alkyl, for example methyl ethyl or tertiarybutyl, or an ammonium or alkali metal ion.

Y is preferably a halogen atom, an alkanesulphonyloxy group (such as methylsulphonyloxy) or arylsulphonyloxy (such as benzenesulphonyloxy or p-toluenesulphonyloxy).

The reaction is preferably carried out in an organic solvent, for example ethan¹, acetonitrile or dimethylformamide, at between room temperature and the boiling point of the solvent. The reaction time may be decreased by employing a catalyst such as

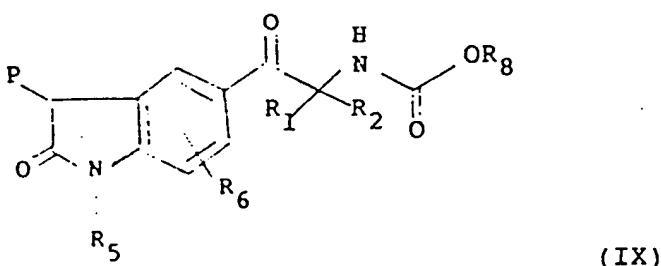
The compounds of formula (IIa) in which W is
 O
 -C- and A is oxygen may be prepared by cyclising a compound of formula (VIII):



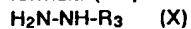
in which R₁, R₂, R₃, R₅ and R₆ are as defined in formula (I), P is as defined in formula (IIa), and R₈ is an alkyl group, preferably C₁₋₆ alkyl such as methyl or ethyl. The cyclisation may be carried out in the presence of a base, such as sodium ethoxide, in a diluent or solvent, such as ethanol, at about ambient temperature.

The compounds of formula (IIa) in which W is

O
 -C- and A is -NH- may be prepared by treating a compound of formula (IX):



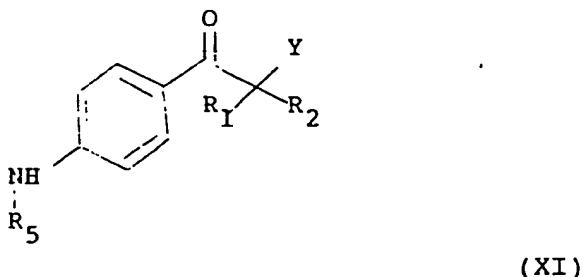
in which R₁, R₂, R₅ and R₆ are as defined in formula (I), P is as defined in formula (IIa), and R₈ is as defined in formula (VIII) with a compound of formula (X):



in which R₃ is as defined in formula (I).

The reaction may be carried out in a diluent or solvent, such as ethanol, and suitably at a temperature up to the boiling point of the diluent or solvent.

The compounds of formula (VI) may themselves be prepared by treating a compound of formula (XI)



in which R₁, R₂, R₅ and Y are as defined in formula (VI) with a compound of formula (Xla):



in which P is as defined in formula (IIa) and R₉ is an alkyl group, preferably C₁₋₆ alkyl.

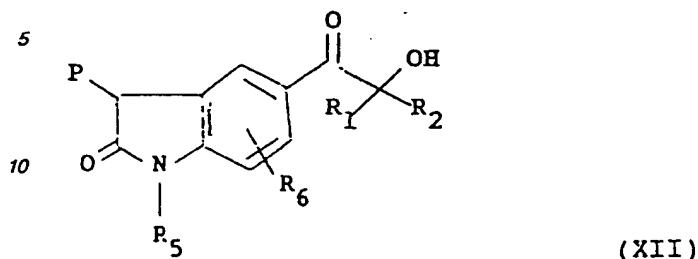
The compounds of formula (XI) are known compounds (Kulkarni et al., J. Pharm. Sci., 58, (7) 852-7, 1969) or can be made from these known compounds by known methods.

The compounds of formula (Xla) are known compounds or are preparable in analogous manner to the known compounds of formula (Xla).

The compounds of formulae (VII) are known compounds, or are preparable in analogous manner to the

known compounds of formula (VII).

Compounds of formula (VIII) may be prepared by treating a compound of formula (XII):

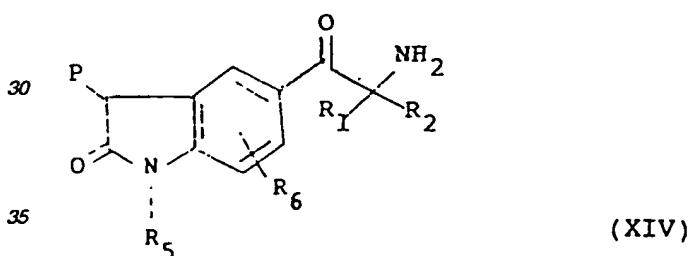


15 in which R₁, R₂, R₅ and R₆ are as defined in formula (I) and P is as defined in formula (IIa), with an alkyl carbazate of formula (XIII):

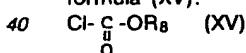


25 in which R₃ and R₈ are as defined in formula (VIII).

Compounds of formula (XII) may themselves be prepared by hydrolysing a compound of formula (VI). Compounds of formula (IX) may be prepared by treating a compound of formula (XIV):



in which R₁, R₂, R₅ and R₆ are as defined in formula (I) and P is as defined in formula (IIa), with a compound of formula (XV):



in which R₈ is as defined in formula (VIII).

Compounds of formula (XIV) may themselves be prepared by treating a compound of formula (VI) with sodium azide, and reducing the thus formed azide with hydrogen in the presence of a palladium/charcoal catalyst.

45 Compounds of formula (X), (XIII) and (XV) are known compounds, or can be prepared from known compounds by known methods.

Intermediate compounds of formula (II) in which W is

50 -C(=O)- are disclosed in EP-A-0303418, and some of those in which W is -CH₂- are generically disclosed in EP-A-0052442.

In general, compounds of formula (II) in which W is -CH₂- may be prepared in an analogous manner to similar compounds which are disclosed in EP-A-0303418 and EP-A-0052442.

55 In order to utilise the potential cardiotonic activity of the compounds of formula (I) the invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusible solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

65 Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants

include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate.

Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved.

Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

In addition such compositions may contain further active agents such as vasodilator agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The invention further provides a method of treatment or prophylaxis of heart disease in mammals, such as humans, which comprises the administration of an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to the sufferer.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the formula (I), the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose may contain from 1 to 1000mg, normally from 1 to 100 mg, for example 2 to 50 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 2,3,4,5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1.0 to 2500 mg, more usually 50 to 2000 mg, for example 10 to 75mg, that is in the range of approximately 0.002 to 35 mg/kg/day, more usually 1 to 30 mg/kg/day, for example 0.15 to 1 mg/kg/day.

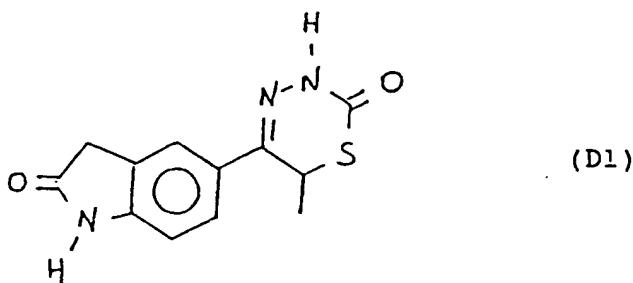
In an additional aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance, and in particular for the treatment of heart disease.

Furthermore, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of heart disease.

The following examples illustrate the preparation of compounds of the invention, the descriptions illustrate the preparation of intermediates, and the pharmacological data illustrate the activity of the compounds of the invention.

Description 1

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2H-indol-2-one



5 A mixture of 38g (0.142mol) 5-(2-bromo-1-oxopropyl)-1,3-dihydro-2H-indol-2-one, 15.04g (0.142mol) methoxy thiocarbonylhydrazine (K.A. Jensen, U. Anthoni, A. Holm, Acta. Chem. Scand., 23, 1916, 1969) in 815ml acetonitrile was refluxed under stirring for 6.5 hours. After cooling in ice, the crude crystalline product was collected, washed with acetonitrile (2x50ml) and dried to give 15.23g of white crystals.

Yield : 41%.

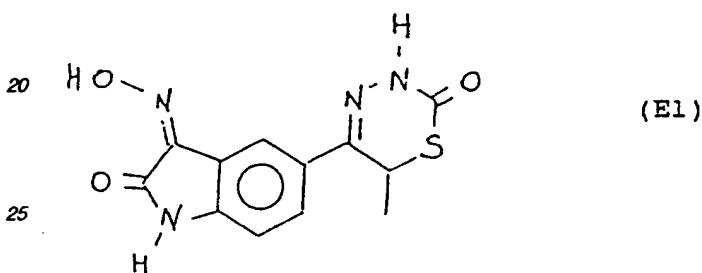
m.p. : 270°C.

IR (KBr): $\nu = 3,450; 3,200; 1,690; 1,640; 1,615; 1,495; 1,250; 1,200 \text{ cm}^{-1}$.

10 NMR (DMSO- d_6): $\delta = 1.47 \text{ ppm (d, } J=7.1 \text{ Hz, 3H, } \text{CH}_3\text{CH)}$; 3.54 (s, 2H, CH_2CO); 4.70 (q, $J=7.1 \text{ Hz, 1H, } \text{CHCH}_3$); 6.89 (d, $J=7.9 \text{ Hz, 1H, Ar}$); 7.66 (d, $J=7.9 \text{ Hz, 1H, Ar}$); 7.68 (s, 1H, Ar); 10.63 (s, 1H, exch. $\text{D}_2\text{O, NH}$); 11.60 (s, 1H, exch. $\text{D}_2\text{O, NH}$).

Example 1

15 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-hydroxyimino-2H-indol-2-one



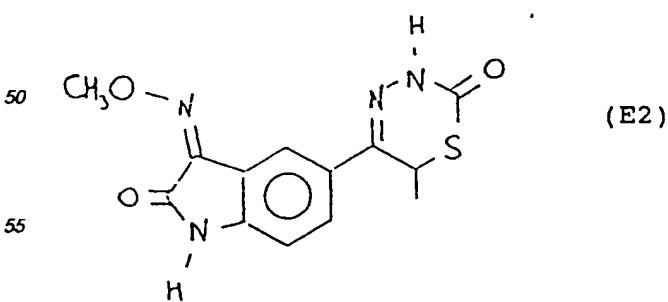
30 A mixture of 2g (7.3mmol) 1,3 dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione, 0.5g (7.3mmol) hydroxylamine hydrochloride, 1g (7.3mmol) potassium carbonate and 50ml ethanol were refluxed for 2 hours. Yellow crystals were filtered off, triturated in water and dried under vacuum. Another crop of yellow crystals were obtained by adding water to the filtrate.

35 Yield : 34%.

m.p. : 170°C. IR (KBr): $\nu = 3,200 \text{ (large); } 1,725; 1,640; 1,615; 1,235 \text{ cm}^{-1}$.
 NMR (DMSO- d_6): $\delta = 1.47 \text{ (d, } J=7.1 \text{ Hz, 3H, } \text{CH}_3\text{-CH)}$; 4.71 (q, $J=7.1 \text{ Hz, 1H, } \text{CH}_3\text{-CH}$); 6.96 (d, $J=8.3 \text{ Hz, 1H, Ar}$); 7.80 (d, $J=8.3 \text{ Hz, 1H, Ar}$); 8.47 (s, 1H, Ar); 10.97 (s, 1H, exch. $\text{D}_2\text{O, NH}$); 11.63 (s, 1H, exch. $\text{D}_2\text{O, NH}$).
 (Multisolv): = 1.54 (d, $J=7.2 \text{ Hz, 3H, } \text{CH}_3\text{-CH}$); 4.53 (q, $J=7.2 \text{ Hz, 1H, } \text{CH}_3\text{-CH}$); 6.93 (d, $J=8.2 \text{ Hz, 1H, Ar}$); 7.75 (dd, $J=8.2 \text{ Hz, } J=1.7 \text{ Hz, 1H, Ar}$); 8.48 (d, $J=1.4 \text{ Hz, 1H, Ar}$); 10.83 (s, 1H, exch. $\text{D}_2\text{O, NH}$); 11.49 (s, 1H, exch. $\text{D}_2\text{O, NH}$); 13.34 (s, 1H, exch. $\text{D}_2\text{O, OH}$).

Example 2

45 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4 thiadiazin-5-yl)-3-methoxyimino-2H-indol-2-one



60 Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4 thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione and methoxylamine and following the method described in example 1, afforded the desired compound.

Yield : 62%.

m.p. : 290°C.

65 IR (KBr): $\nu = 3,300; 1,745; 1,718; 1,615; 1,585; 1,295; 1,080; 1,025 \text{ cm}^{-1}$.

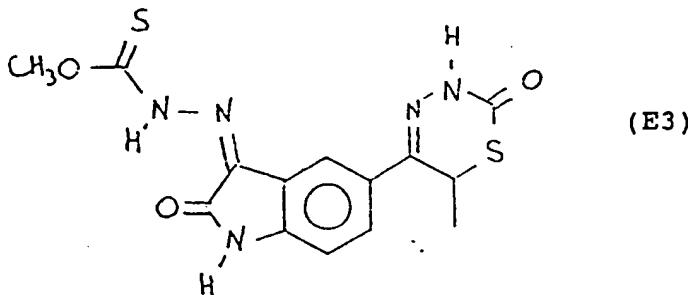
NMR (DMSO-d₆): δ = 1.48 (d, J = 7.1Hz, 3H, CH₃CH); 4.23 (s, 3H, CH₃O); 4.72 (q, J = 7.1Hz, 1H, CH₃-CH); 6.98 (d, J = 8.2Hz, 1H, Ar); 7.84 (dd, J = 8.2Hz, J' = 1.5Hz, 1H, Ar); 8.30 (d, J' = 1.5Hz, 1H, Ar); 11.07 (s, 1H, exch.D₂O, NH); 11.68 (s, 1H, exch.D₂O, NH).

Example 3

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O-Methyl
2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]-hydrazine
carbothioate

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A mixture of 1g (3.6mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione, 0.38g (3.6mmol) methoxythiocarbonyl hydrazine in 30ml ethanol were refluxed for 30 minutes. After cooling, filtration afforded the desired compound.

Yield : 71% (950mg). orange crystals.

m.p. : 245°C.

IR (KBr): ν = 3,200; 3,150; 1,700; 1,650; 1,620; 1,490; 1,450; 1,305; 1,220; 1,155 cm⁻¹.

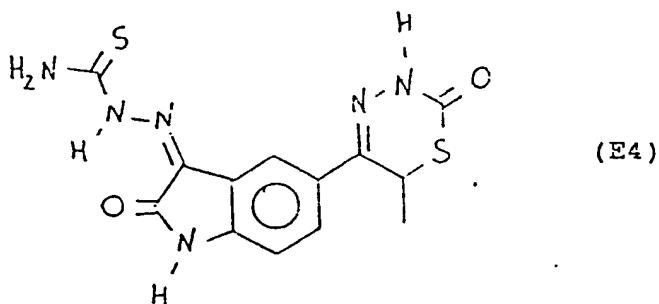
NMR (DMSO-d₆): δ = 1.47 ppm (d, J = 7.1Hz, 3H, CH₃CH); 4.17 (s, 3H, CH₃O); 4.83 (q, J = 7.1Hz, 1H, CH₃-CH); 7.03 (d, J = 8.3Hz, 1H, Ar); 7.87 (dd, J = 8.3Hz, J' = 1.8Hz, 1H, Ar); 7.93 (s, 1H, Ar); 11.57 (s, 1H, exch.D₂O, NH); 11.69 (s, 1H, exch.D₂O, NH); 13.51 (s, 1H, exch.D₂O, NH).

Example 4

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2-[2,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]-hydrazine
carbothioamide.

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A mixture of 1g (3.6mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione, 0.33g (3.6mmol) thiosemicarbazide in 30ml ethanol were refluxed for 30 minutes. Filtration of the cooled resulting suspension, yielded the desired compound as yellow crystals.

Yield : 79%.

m.p. : 300°C.

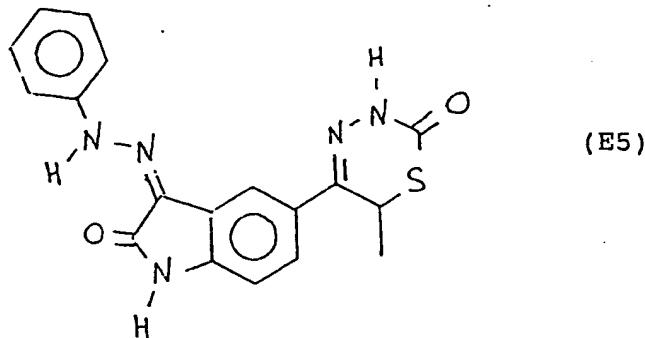
IR (KBr): ν = 3,250; 1,698; 1,648; 1,625; 1,608; 1,590; 1,485; 1,210; 1,140 cm⁻¹.

NMR (DMSO-d₆): δ = 1.52 (d, J = 7.1Hz, 3H, CH₃-CH); 4.65 (q, J = 7.1Hz, 1H, CHCH₃); 7.02 (d, J = 8.3Hz, 1H, Ar); 7.81 (dd, J = 8.3Hz, J' = 1.7Hz, 1H, Ar); 8.12 (d, J' = 1.4Hz, 1H, Ar); 8.81 (s, 1H, exch.D₂O, NH); 9.12 (s, 1H, exch.D₂O, NH); 11.43 (s, 1H, exch.D₂O, NH); 11.70 (s, 1H, exch.D₂O, NH); 12.41 (s, 1H, exch.D₂O, NH).

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Example 55-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-phenylhydrazone :

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A mixture of 1g (3.6mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione, 0.4g (3.7mmol) phenylhydrazine in 30ml ethanol was refluxed for 15 minutes. Filtration yielded 950mg yellow crystals which were purified by column chromatography on silica (eluent : chloroform with 1% methanol).

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Yield : 770mg (58%).
m.p. : 296°C.

IR (KBr): $\nu = 3,150; 1,692; 1,615; 1,595; 1,560; 1,240; 1,150 \text{ cm}^{-1}$.

NMR (DMSO- d_6): $\delta = 1.50 \text{ ppm}$ ($d, J = 7.1 \text{ Hz}, 3\text{H}, \text{CH}_3\text{-CH}$); 4.83 ($q, J = 7.1 \text{ Hz}, 1\text{H}, \text{CH}_3\text{CH}$); 6.9-8.1 ($m, 8\text{H}, \text{Ar}$); 11.26 ($s, 1\text{H}, \text{exch. D}_2\text{O, NH}$); 11.64 ($s, 1\text{H}, \text{exch. D}_2\text{O, NH}$); 12.74 ($s, 1\text{H}, \text{exch. D}_2\text{O, NH-N}$).

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Alternative preparation

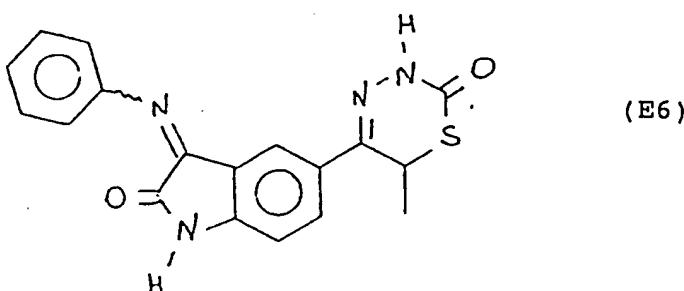
400mg (4.3mmol) aniline in 10ml water containing 2.5ml hydrochloric acid were diazotized at 0.5°C with a cold solution of 300mg (4.3mmol) sodium nitrite in 8ml water. This solution was added dropwise to a solution of 1.0g (3.0mmol) 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one in 20ml ethanol and 20ml DMF. The mixture was stirred 1 hour at room temperature. The precipitate was filtered off, washed with methylene chloride and methanol- and dried under vacuum.
m.p., IR, NMR were identical to those of the product obtained by the previous method.

Example 6

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1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one

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A mixture of 2g (7.3mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione and 0.68g (7.3mmol) aniline in 50ml ethanol was refluxed for 1 hour. After cooling, yellow crystals were filtered off and dried at 40°C under vacuum.

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Yield : 78% (as a mixture syn + anti).

m.p. : 290°C.

IR (KBr): $\nu = 3,200; 1,769; 1,735; 1,645; 1,615; 1,485; 1,305; 1,205 \text{ cm}^{-1}$.

NMR (DMSO- d_6): mixture of syn + anti: $\delta = 1.27 \text{ ppm}$ ($d, J = 7.1 \text{ Hz}, 3 \times 0.72\text{H}, \text{CH}_3\text{-CH}$); 1.48 ($d, J = 7.1 \text{ Hz}, 3 \times 0.28\text{H}, \text{CH}_3\text{CH}$); 4.07 ($q, J = 7.1 \text{ Hz}, 0.72\text{H}, \text{CH}_3\text{CH}$); 4.80 ($q, J = 7.1 \text{ Hz}, 0.28\text{H}, \text{CH}_3\text{CH}$); 6.7-8.1 ($m, 8\text{H}, \text{Ar}$); 11.2 ($m, 1\text{H}, \text{exch. D}_2\text{O, NH}$); 11.57 ($m, 0.72\text{H}, \text{exch. D}_2\text{O, NH}$); 11.68 ($m, 0.28\text{H}, \text{exch. D}_2\text{O, NH}$).

MS : 18,28,51,77,218,233,234,235,261,262,322,323,350,351, 352. Molecular ion : 350.0823 (Theoretical
350.08374 for C₁₈H₁₄N₄O₂S).

Alternative method
20g (76mmoles) 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one in
700ml 1/1 methanol/ethanol were heated to 60° C. 9g (8.3 mmoles) nitrosobenzene were added portionwise.
then 4ml piperidin dropwise. 1h suspension became clear, then a precipitate appeared after a few minutes.
Stirring was continued for 10 minutes, and the suspension cooled. The precipitate was filtered off, washed with
methylene chloride and dried under vacuum, yielding 15.5g (58%) of the desired compound, identical to that
obtained by the previous method.

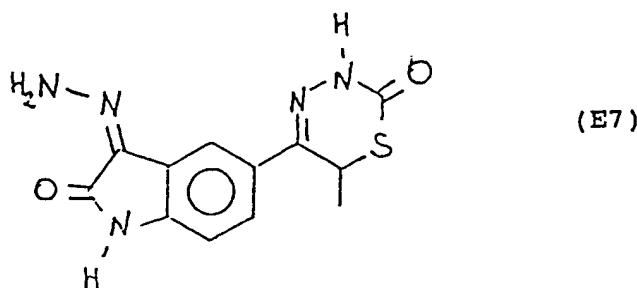
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Example 75-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-Indole-2,3-dione 3-hydrazone

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1g (3.6mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione
were added to a solution of 10ml hydrazine hydrate in 10ml ethanol at room temperature. The color changed
from red to yellow. 60ml water were added. After filtration, 150mg of yellow crystals were isolated.

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Yield : 14%.

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m.p. : 268°C.

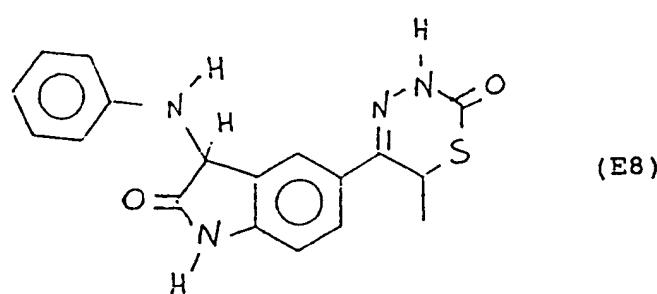
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IR (KBr): $\nu = 3,400; 3,200; 1,690; 1,620; 1,600; 1,480; 1,190 \text{ cm}^{-1}$.
NMR (DMSO- d_6): $\delta = 1.48 \text{ ppm}$ (d, $J = 7.1 \text{ Hz}$, 3H, CH_3-CH); 4.77 (q, $J = 7.1 \text{ Hz}$, 1H, CH_3-CH); 6.95
(d, $J = 8.3 \text{ Hz}$, 1H, Ar); 7.65 (dd, $J = 8.3 \text{ Hz}, J' = 1.7 \text{ Hz}$, 1H, Ar); 7.79 (d, $J' = 1.7 \text{ Hz}$, 1H, Ar); 9.80
(m, 1H, exch. $\text{D}_2\text{O}, \text{NH}_2$); 10.52 (m, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 10.93 (m, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 11.60 (m, 1H, exch. $\text{D}_2\text{O}, \text{NH}$).

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Example 81,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one,
hydrochloride

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1g (2.8mmol) 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-
2-one (E6) and 1.87g (28mmol) powdered zinc in 20ml glacial acetic acid were refluxed for 10 minutes. The
excess of zinc was removed by filtration and washed with acetic acid. 100ml water were added to the filtrate
and the precipitate was filtered, washed with water until neutral, and dried under vacuum. This compound was
kept under argon since it reverts to the starting material in presence of air.
The crystals of the free base were suspended in a 1/5 mixture of methanol/ethyl ether (30ml) and about 5ml of
a saturated solution of HCl gas in ethyl ether were added. After 1 hour of stirring, the white precipitate was

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filtered off, washed with ether and dried.

Overall yield : 730mg (66%).

m.p. : 335°C (hydrochloride); 164°C dec (free base).

Hydrochloride : IR (KBr): $\nu = 3,400; 3,200; 1,735; 1,625; 1,500 \text{ cm}^{-1}$.

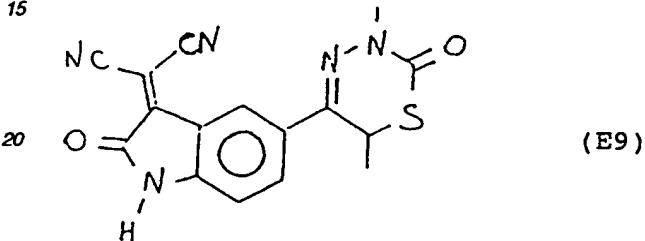
5 NMR (DMSO-d₆): $\delta = 1.43$ ppm (d,J=7.1Hz,3H,CH₃-CH); 3.38 (q, J=7.1Hz,1H,CH₃-CH); 5.17 (s,1H,NHCH); 5.36 (m,exch.D₂O,HCl+NH Ar); 6.5-6.6 (m,3H,Ar); 6.9-7.1 (m,3H,Ar); 7.6-7.7 (m,2H, Ar); 10.81 (s,1H,exch.D₂O,NH); 11.55 (s,1H,exch.D₂O,NH).

Example 9

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[5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,2-dihydro-2-oxo-3H-indol-3-ylidene]-propane-dinitrile

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30 500mg (1.8mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3 (1H)-dione, 0.73g (6ep.) malononitrile in 50ml ethanol were stirred at room temperature for 0.5 hour. The precipitate was filtered and dried under vacuum. Dark violet crystals.

Yield : 73%.

m.p. : 276°C.

IR (KBr): $\nu = 3,450; 3,100; 2,240$ (weak); 1,745; 1,642; 1,622; 1,600; 1,305; 1,205 cm^{-1} .

35 NMR (DMSO-d₆): $\delta = 1.49$ ppm (d,3H,J=7.2Hz,CH₃-CH); 4.68 (q,1H,J=7.2Hz,CH₃CH); 7.02 (d,1H,J=8.4Hz,Ar); 7.94 (dd,J=8.4Hz,J'=1.2Hz,1H,Ar); 11.47 (s,1H,exch.D₂O,NH); -1.77 (s,1H,exch.D₂O,NH).

Example 10

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1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylmethylen-2H-indol-2-one

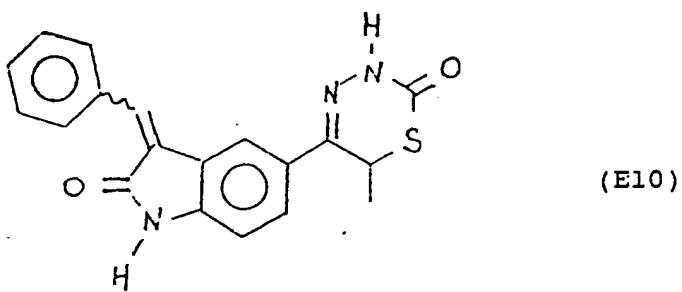
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A mixture of 1g (3.8mmol) 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-3,3-dimethyl-2H-indol-2-one, 0.4g (3.8mmol) benzaldehyde and 0.05g (0.5mmol) piperidine in 5ml methanol was refluxed with stirring for 45 minutes. After cooling at room temperature a precipitate was collected, washed with methanol and dried to give 1.1g of yellow crystals.

Yield : 83%.

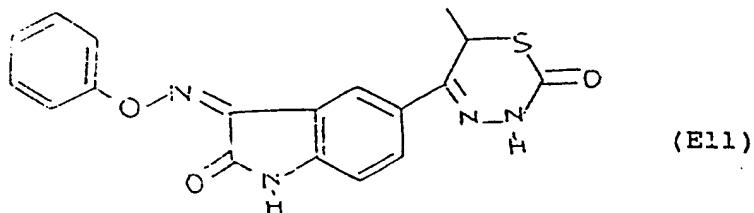
m.p. : 263°C.

IR (KBr) : v: 3,300; 1,690; 1,650; 1,615; 1,200 cm⁻¹.

NMR (DMSO-d₆): mixture of E/Z (about 70/30) δ = 1.44 ppm (d,J=7.1Hz,3x0.7H,CH₃CH); 1.53 (d,J=7.1Hz,3x0.3H,CH₃CH); 4.51 (q,J=7.1Hz,0.7H,CHCH₃); 4.77 (q,J=7.1Hz,0.3H,CHCH₃); 6.90-8.45 (m,9H,Ar and Ar-CH=); 10.91 (s,0.3+0.7H,exch. D₂O,NH); 11.57 (s,0.7H,exch.D₂O,NH); 11.66 (s,0.3H,exch. D₂O,NH).

Example 11

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenoxyimino-2H-indol-2-one



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3(1H)-dione and phenoxyamine, and following the method described in Example 1, the desired compound was obtained.

Yield : 41%.

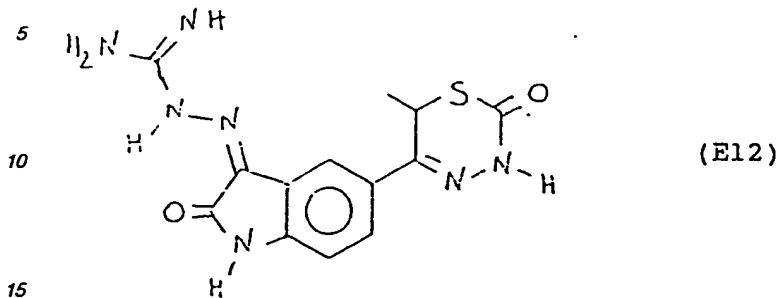
m.p. : 212°C.

IR (KBr) : v = 1,735; 1,615; 1,595; 1,485; 1,300; 1,195 cm⁻¹.

NMR (DMSO-d₆): δ = 1.51 (d,J=7Hz,3H,CH₃CH); 4.79 (q,J=7Hz,1H,CHCH₃); 7.04 (d,J=8Hz,1H,Ar); 7.2-7.6 (m,5H,Ar phenyl); 7.94 (dd,J=8Hz,J'=1.7Hz,1H,Ar); 8.51.. (d,J'=1.7Hz,1H,Ar); 11.2 (m,1H,exch.D₂O,NH); 11.7 (m,1H,exch.D₂O,NH).

Example 12

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione
3-[2-(aminomethanimino)hydrazone]

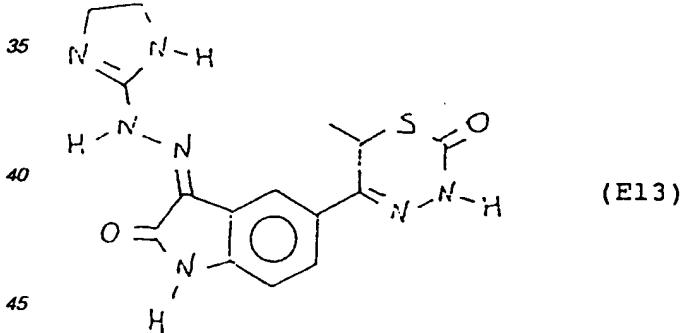


Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3(1H)-dione and aminoguanidine bicarbonate and following the method described in Example 1, the desired compound was obtained.

Yield : 47%.
m.p. : 225°C dec.
IR (KBr) : ν = 3,300; 1,690; 1,610; 1,470; 1,430 cm^{-1} .
NMR (DMSO-d₆) : δ = 1.47 (d, J = 7.1Hz, 3H, CH₃CH); 4.67 (q, J = 7.1Hz, 1H, CH₃CH); 6.76 (s, 3H, exch.D₂O NH, NH₂); 6.88 (d, J = 8.2Hz, 1H, Ar); 7.68 (dd, J = 8.2Hz, J' = 1.8Hz, 1H, Ar); 8.74 (d, J' = 1.8Hz, 1H, Ar); 10.48 (s, 1H, exch.D₂O, NH); 11.56 (s, 1H, exch.D₂O, NH).

Example 13

30 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione
3-[2-(4,5-dihydro-1H-2-imidazolyl)hydrazone]

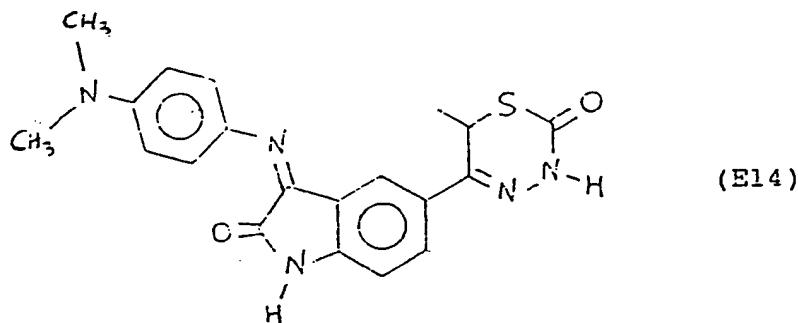


Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3(1H)-dione and 2-hydrazino-2-imidazolin hydrobromide and following the method described in Example 1, the desired compound was obtained.

Yield : 41%.
m.p. : 243°C dec.
IR (KBr) : ν : 1,680; 1,610; 1,510; 1,165 cm^{-1} .
NMR (DMSO-d₆) : δ = 1.49 (d, J = 7.1Hz, 3H, CH₃CH); 3.34 (s, 4H, NCH₂CH₂N); 4.58 (q, J = 7.1Hz, 1H, CH₃CH); 6.88 (d, J = 8.3Hz, 1H, Ar); 7.5-7.7 (m, containing at 7.63, s, 2H, exch.D₂O, NH, NH₂; and dd, J = 8.3Hz, J' = 1.7Hz, 1H, Ar); 8.72 (d, J' = 1.7Hz, 1H, Ar); 10.50 (s, 1H, exch.D₂O, NH); 11.58 (s, 1H, exch.D₂O, NH).

60 Example 14

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(4-dimethylaminophnylimino)-2H-indol-2-one



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3(1H)-dione and N,N-dimethyl p-phenylene diamine and following the method described in Example 1, the desired compound was obtained.

Yield : 81%.

m.p. : 261°C

IR (KBr) : $\nu = 3,200; 1,740; 1,610; 1,565 \text{ cm}^{-1}$.

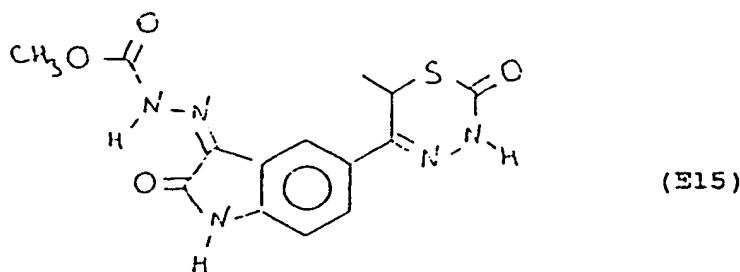
NMR (DMSO-d₆): Mixture of two isomers in a ratio of about 45/55

A (major isomer) : 1.36 (d,J=7.2Hz,3H,CH₃CH); 2.99 (s,6H,CH₃NCH₃); 4.30 (q,J=7.2Hz,1H,CH₃CH); 6.6-8.0 (m,7H,Ar); 11.10 (m,1H,exch.D₂O,NH); 11.65 (m,1H,exch. D₂O,NH).

B (minor isomer) : 1.48 (d,J=7.1Hz,3H,CH₃CH); 3.02 (s,6H,CH₃NCH₃); 4.79 (q,J=7.1Hz,1H,CH₃CH); 6.6-8.0 (m,7H,Ar); 11.10 (m,1H,exch.D₂O,NH); 11.65 (m,1H,exch. D₂O,NH).

Example 15

Methyl 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazine carboxylate



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3H-indole-2,3(1H)-dione and methylcarbazate and following the method described in Example 1, the desired compound was obtained.

Yield : 33%.

m.p. : 201°C

IR (KBr) : $\nu = 3,200; 1,735; 1,610; 1,525; 1,180 \text{ cm}^{-1}$.

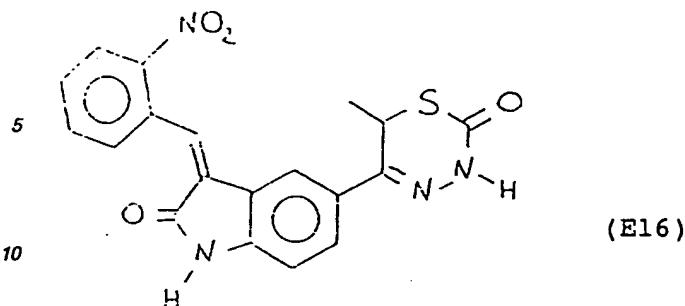
NMR (DMSO-d₆): $\delta = 1.50$ (d,J=7.0Hz,3H,CH₃CH); 3.84 (s,3H, CH₃O); 4.81 (q,J=7.0Hz,1H,CH₃CH); 6.97 (d,J=8.3Hz,1H,Ar); 7.84 (d,J=8.3Hz,1H,Ar); 8.34 (s,1H, Ar); 11.02 (s,1H,exch.D₂O,NH); 11.25 (s,1H,exch.D₂O,NH); 11.70 (s,1H,exch.D₂O,NH).

Example 16

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-nitrophenylmethylen)-2H-indol-2-one

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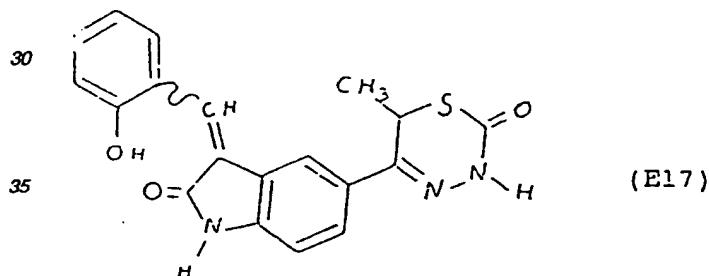
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15 Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one and 2-nitro benzaldehyde and following the method described in Example 10, the desired compound was obtained. Yield : 33%.
 m.p. : 258°C
 IR (KBr) : ν = 3,200; 1,710; 1,645; 1,605; 1,520 cm⁻¹.
 20 NMR (DMSO- d_6) : δ = 1.33 (d,J=7.1Hz,3H, CH_3CH); 4.35 (d,J=7.1Hz,1H, CH_3CH); 6.9-8.4 (m,8H including 1H vinyl at 7.33 ppm,3H,Ar and 4H phenyl ring); 10.97 (s,1H, exch. $\text{D}_2\text{O},\text{NH}$); 11.53 (s,1H,exch. $\text{D}_2\text{O},\text{NH}$).

Example 17

25 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-[(2-hydroxyphenyl)methylene]-2H-indol-2-one



Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one and 2-hydroxy benzaldehyde and following the method described in Example 10, the desired compound was obtained.
 Yield : 62%.
 m.p. : 233°C
 IR (KBr) : ν = 3,200; 1,680; 1,640; 1,610; 1,455; 1,225 cm^{-1} .
 NMR (DMSO-d₆) : δ = 1.45 (d,J=7.1Hz,3H,CH₃CH); 4.50 (q,J=7.1Hz,3H,CH₃CH); 6.9-8.1 (m,8H Including 4H phenyl, 3H,Ar and 1H,vinylic); 10.26 (m,1H,exch.D₂O,OH); 10.82 (s,1H,exch.D₂O,NH); 11.55 (s,1H exch D₂O,NH).

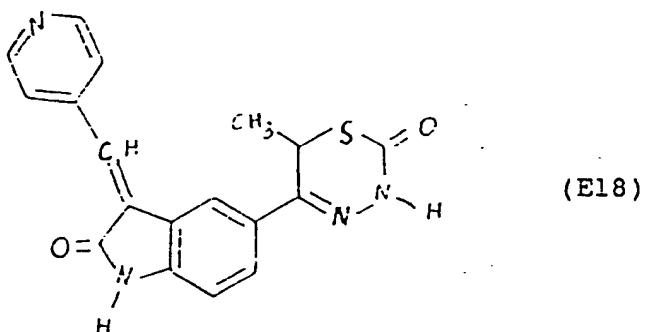
Example 18

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(4-pyridylmethylene)-2H-indol-2-one

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Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one and pyridine 4-carboxaldehyde and following the method described in Example 10, the desired compound was obtained.

Yield : 85%.

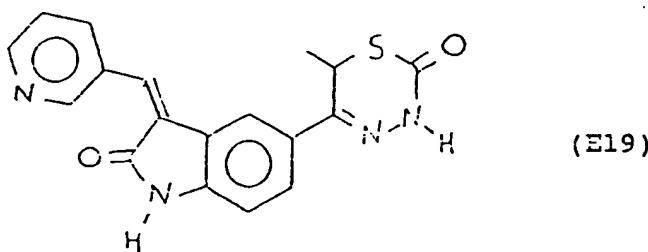
m.p. : 319°C

IR (KBr) : $\nu = 1,690; 1,600; 1,200 \text{ cm}^{-1}$

NMR (DMSO- d_6) : $\delta =$ mixture of two isomers Z and E in a ratio of about 40/60
1.42 ($d, J=6.3\text{Hz}, 3\text{H}, \text{CH}_3\text{CH}$, major isomer); 1.52 ($d, J=6.3\text{Hz}, 3\text{H}, \text{CH}_3\text{CH}$, minor isomer); 4.52 ($q, J=6.3\text{Hz}, 1\text{H}, \text{CH}_3\text{CH}$, major isomer); 4.75 ($q, J=6.3\text{Hz}, 1\text{H}, \text{CH}_3\text{CH}$, minor isomer); 6.9-8.8 (m, 8H including 1H, vinylic, 3H, Ar and 4H, pyridine); 10.98 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 11.57 and 11.67 (2s, 1H, exch. $\text{D}_2\text{O}, \text{NH}_2$ isomers).

Example 19

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(3-pyridylmethylen)-2H-indol-2-one

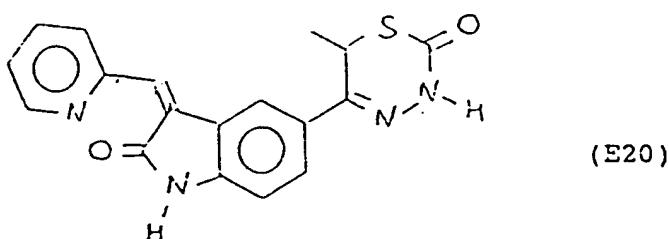


Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one and pyridine 3-carboxaldehyde and following the method described in Example 10, the desired compound was obtained.

Yield : 75%. m.p. : 285°C IR (KBr) : $\nu = 1,690; 1,650; 1,615; 1,210 \text{ cm}^{-1}$. NMR (DMSO- d_6) : mixture E + Z in a ratio of about 1 to 1. 1.43 ($d, J=6.7\text{Hz}, 3\text{H}, \text{CH}_3\text{CH}$, isomer A); 1.53 ($d, J=6.7\text{Hz}, 3\text{H}, \text{CH}_3\text{CH}$, isomer B); 4.52 ($q, J=6.7\text{Hz}, 1\text{H}, \text{CH}_3\text{CH}$, isomer A); 4.76 ($q, J=6.7\text{Hz}, 1\text{H}, \text{CH}_3\text{CH}$, isomer B); 6.9-9.3 (m, 8H including 1H vinyl, 4H pyridine and 3H Ar); 10.96 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 11.57 and 11.67 (2s, 1H, exch. $\text{D}_2\text{O}, \text{NH}_2$ isomer A and B).

Example 20

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-pyridylmethylen)-2H-indol-2-one



Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indole-2-one and pyridine 2-carboxaldehyde and following the method described in Example 10, the desired compound was obtained.

Yield : 77%.

m.p. : 296°C

IR (KBr) : ν = 3,150; 1,700; 1,635; 1,610 cm⁻¹.

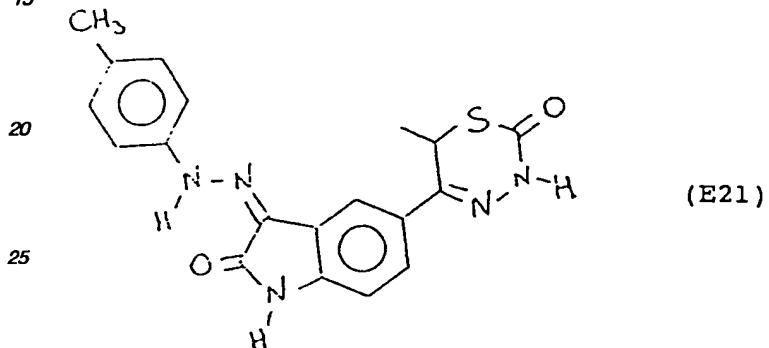
NMR (DMSO-d₆) : δ = 1.61 (d,J=7.1Hz,3H,CH₃CH); 4.69 g,J=7.1Hz,1H,CH₃CH); 6.96 (d,J=8.3Hz,1H,Ar); 7.48-8.04 (m,5H including 2H Ar, 1H vinylic and 2H pyridine); 8.9-9.0 (m,1H,pyridine); 9.74 (s,1H,pyridine); 10.91 (s,1H,exch.D₂O,NH); 11.64 (s,1H,exch.D₂O,NH).

10

Example 21

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-methyl)phenylhydrazone]

15



30

A mixture of 1.5 g (4.3 mmol) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 0.75g (4.5 mmol) 4 methylphenylhydrazine in 20 ml acetonitrile was refluxed 2 hours. The mixture was cooled, filtered off and the residue was washed with hot 1/1 methanol/water. After drying under vacuum orange crystals were obtained. Yield : 92%

35

m.p. : 285°C

IR (KBr) : ν = 1,680; 1,620; 1,550; 1,240 cm⁻¹.

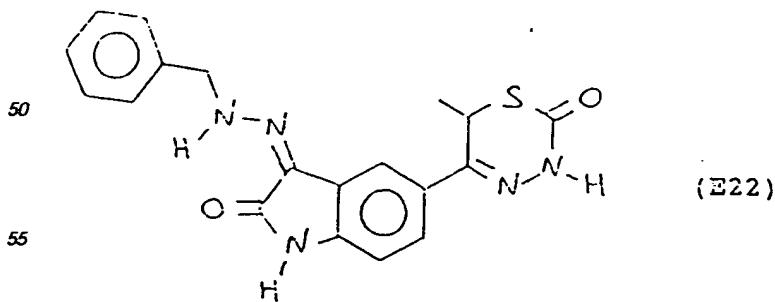
NMR (DMSO-d₆) : δ = 1.50 (d,J=7.1Hz,3H,CH₃CH); 2.29 (s,3H,CH₃Ar); 4.85 (q,J=7.1Hz,1H,CH₃CH); 7.00 (d,J=8.3Hz,1H,Ar); 7.20 (d,AB,J=8.4Hz,2H,phenyl); 7.39 (d,AB,J=8.4Hz,2H,phenyl); 7.73 (dd,J=8.3Hz,J'=1.8Hz,1H, Ar); 7.99 (d,J=1.8Hz,1H,Ar); 11.26 (s,1H,exch.D₂O,NH); 11.66 (s,1H,exch.D₂O,NH); 12.74 (s,1H,exch.D₂O,NH).

40

Example 22

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(phenylmethyl)hydrazone]

45



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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and benzylhydrazine dihydrochloride and following the method described in Example 21, the desired compound was obtained.

Yield : 24%

m.p. : 202°C

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65 IR (KBr) : ν = 3,200; 1,665; 1,605; 1,550 cm⁻¹.

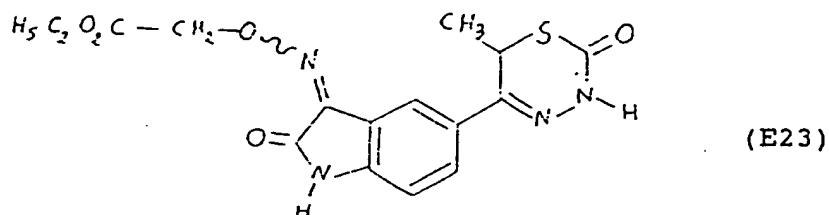
NMR (DMSO-d₆): δ = 1.46 (d,J=7.0Hz,3H,CH₃CH); 4.7-4.8 (m,3H,ArCH₂ + CHCH₃); 6.94 (d,J=8.3Hz,1H,Ar); 7.2-7.4 (m,5H,phenyl ring); 7.64 (d,J=8.3Hz,1H,Ar); 7.80 (s,1H, Ar); 11.03 (s,1H,exch.D₂O,NH); 11.37 (s,1H,exch.D₂O,NH); 11.61 (s,1H,exch.D₂O,NH).

Example 23

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Ethyl[[[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]amino]oxy]acetate

10



15

Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and ethyl aminoxyacetate and following the method described in Example 21, the desired compound was obtained.

20

Yield : 64%

25

m.p. : 118°C

IR (KBr) : ν = 3,200; 1,740; 1,610; 1,210 cm⁻¹.

30

NMR (CDCl₃): δ = 1.32 (t,J=7.2Hz,3H,CH₃CH₂O); 1.67 (d,J=7.2Hz,3H,CH₃CH); 4.1-4.4 (m,q + t,3H,CH₃CH₂O and CH₃CH); 5.07 (s,2H,OCH₂CO); 6.97 (d,J = 8.4Hz,1H,Ar); 7.77 (dd,J=8.4Hz,J'=1.9Hz,1H,Ar); 8.40 (d,J'=1.9Hz,1H, Ar); 9.10 (m,2H,exch.D₂O,NH,NH).

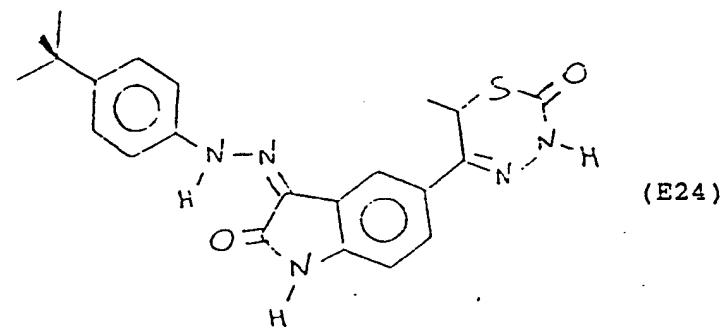
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Example 24

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5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione
3-[4-(1,1-dimethylethyl)phenylhydrazone]

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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 4t-butyl phenylhydrazine hydrochloride and following the method described in Example 21, the desired compound. was obtained.

55

Yield : 83%

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m.p. : 299°C

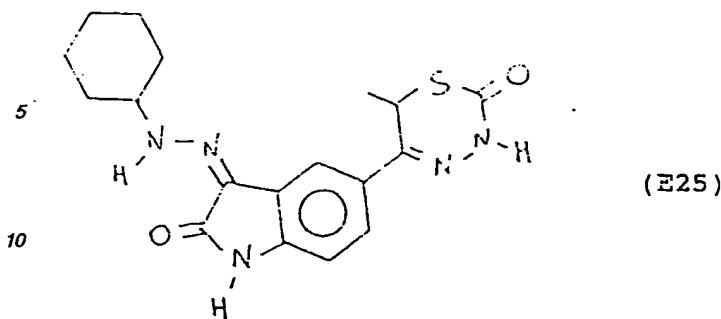
IR (KBr) : ν = 3,200; 1,680; 1,635; 1,615; 1,550; 1,180 cm⁻¹.

NMR (DMSO-d₆): δ = 1.29 (s,9H,t-Bu); 1.50(d,J=7.1Hz,3H, CH₃CH); 4.82 (q,J=7.1Hz,1H,CH₃CH); 7.00 (d,J=8.3Hz,1H, Ar); 7.41 (s,4H,ArBu); 7.72 (d,J=8.3Hz,1H,Ar); 7.99 s,1H,Ar); 11.26 (s,1H,exch.D₂O,NH); 11.66 (s,1H,exch. D₂O,NH); 12.77 (s,1H,exch.D₂O,NH).

Example 25

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5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(cyclohexylhydrazone)



15 Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and cyclohexylhydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 54%

m.p. : 217°C

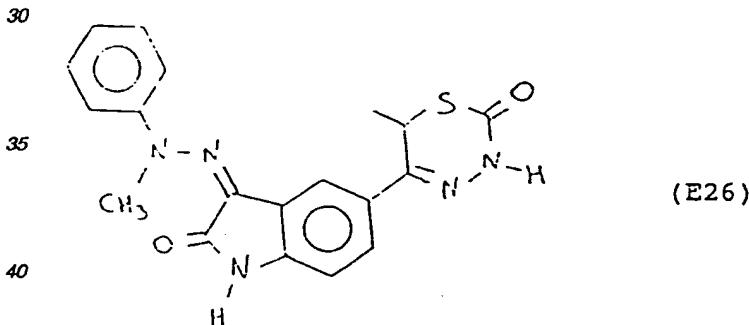
20 IR (KBr) : $\nu = 3,150; 1,675; 1,635; 1,545; 1,190 \text{ cm}^{-1}$.

NMR (DMSO-d₆) : $\delta = 1.0\text{-}2.1$ (m,13H,including cyclohexyl ring and d, at 1.47 ppm, J=7.1Hz,3H,CH₃CH); 3.5-3.7 (m, 1H,CHNH); 4.78 (q,J=7.1Hz,1H,CH₃CH); 6.95 (d,J=8.2Hz, 1H,Ar); 7.64 (dd,J=8.2Hz,J'=1.6Hz,1H,Ar); 7.80 (d, J'=1.6Hz,1H,Ar); 11.03 (s,1H,exch.D₂O,NH); 11.16 (d, J=5.3Hz,1H,exch.D₂O,NH); 11.61 (s,1H,exch.D₂O,NH).

25

Example 26

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(methylphenylhydrazone)



45 Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 1-methyl 1-phenylhydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 47%

m.p. : 260°C

50 IR (KBr) : $\nu = 1,690; 1,605; 1,540; 1,490 \text{ cm}^{-1}$.

NMR (DMSO-d₆) : $\delta = 1.49$ (d,J=7.1Hz,3H,CH₃CH); 3.91 (s,3H,NCH₃); 4.83 (q,J=7.1Hz,1H,CH₃CH); 6.9-8.0 (m,8H,including 5H,phenyl ring and 3H,Ar); 11.1 (m,1H,exch.D₂O,NH); 11.6 (m,1H,exch.D₂O,NH).

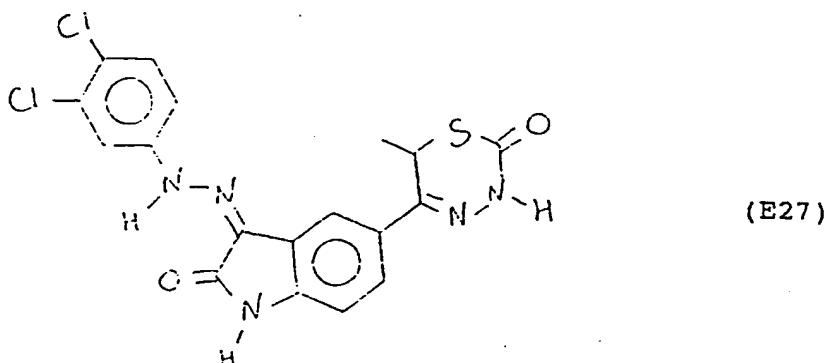
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Example 27

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(3,4-dichlorophenyl)hydrazone]

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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 3,4-dichlorophenyl hydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 53%

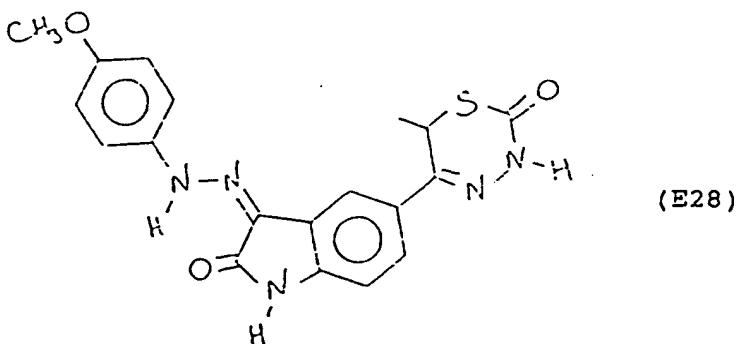
m.p. : 295°C

IR (KBr) : ν = 1,675; 1,625; 1,560; 1,475 cm⁻¹.

NMR (DMSO-d₆) : δ = 1.49 (d,J=7.1Hz,3H,CH₃CH); 4.84 (q,J=7.1Hz,1H,CH₃CH); 7.00 (d,J=8.3Hz,1H,Ar); 7.4-7.8 (m,4H,3H phenyl ring + 1H Ar); 8.02 (s,1H,Ar); 11.32 (s,1H,exch.D₂O,NH); 11.67 (s,1H,exch.D₂O,NH); 12.63 (s, 1H,exch.D₂O,NH).

Example 28

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-methoxy)phenyl]hydrazone]



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 4-methoxyphenyl hydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 90%

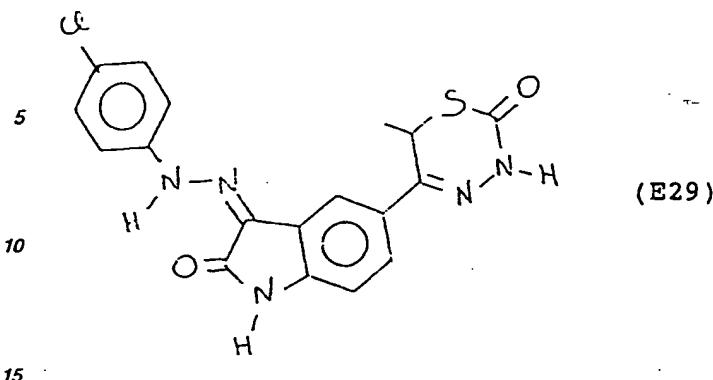
m.p. : 273°C

IR (KBr) : ν = 3,200; 1,680; 1,645; 1,620; 1,560 cm⁻¹.

NMR (DMSO-d₆) : δ = 1.50 (d,J=7.0Hz,3H,CH₃CH); 3.76 (s,3H,CH₃O); 4.83 (q,J=7.0Hz,1H,CH₃CH); 6.9-7.1 (m,3H 2H phenyl + 1H Ar); 7.43 (d,AB,J=9.0Hz,2H,phenyl); 7.71 dd,J=8.3Hz,J'=1.7Hz,1H,Ar); 7.98 (d,J'=1.7Hz,1H,Ar); 11.22 (s,1H,exch.D₂O,NH); 11.65 (s,1H,exch.D₂O,NH); 12.77 (s,1H,exch.D₂O,NH).

Example 29

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-chlorophenyl)phenyl]hydrazone]



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indole-2-one, and 4-chlorophenyl hydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 70%

20 m.p. : 283°C

IR (KBr) : $\nu = 1,690; 1,620; 1,560 \text{ cm}^{-1}$.

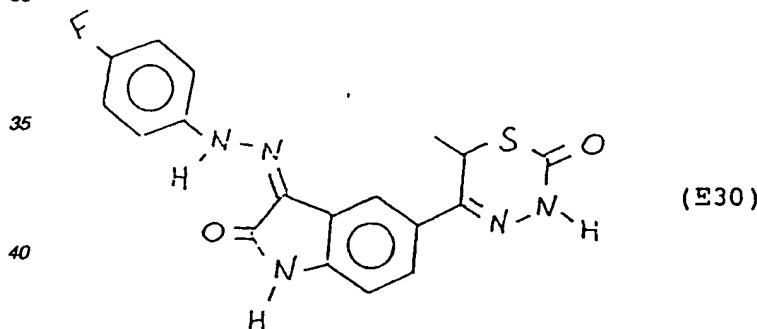
NMR (DMSO- d_6) : $\delta = 1.50$ (d, $J=7.0\text{Hz}$, 3H, CH_3CH); 4.84 (q, $J=7.0\text{Hz}$, 1H, CH_3CH); 7.01 (d, $J=8.3\text{Hz}$, 1H, Ar); 7.4-7.6 (m, 4H, phenyl); 7.75 (dd, $J=8.3\text{Hz}, J=1.2\text{Hz}$, 1H, Ar); 8.00 (d, $J'=8.2\text{Hz}$, 1H, Ar); 11.30 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 11.67 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 12.69 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$).

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Example 30

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-fluorophenyl)hydrazone]

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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indole-2-one, and 4-fluorophenyl hydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 64% m.p. : 291°C

50 IR (KBr) : $\nu = 3,200; 1,695; 1,620; 1,565, 1,520; 1,150 \text{ cm}^{-1}$.

NMR (DMSO- d_6) : $\delta = 1.50$ (d, $J=7.0\text{Hz}$, 3H, CH_3CH); 4.84 (q, $J=7.0\text{Hz}$, 1H, CH_3CH); 7.01 (d, $J=8.3\text{Hz}$, 1H, Ar); 7.24-7.29 (m, 2H, phenyl); 7.50-7.60 (m, 2H, phenyl); 7.74 (d, $J=8.3\text{Hz}$, 1H, Ar); 8.00 (s, 1H, Ar); 11.28 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 11.67 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 12.70 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$).

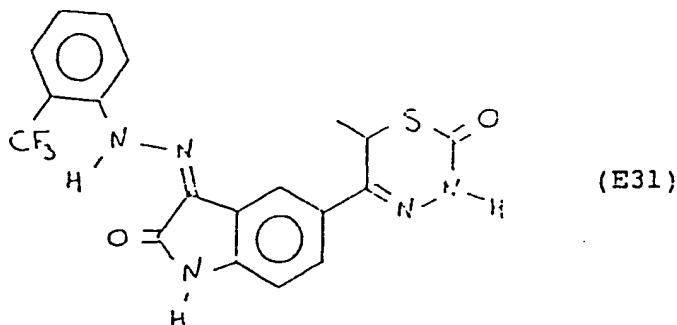
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Example 31

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(2-trifluoromethyl)phenylhydrazone]

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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 2-trifluoromethyl phenyl hydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 44%

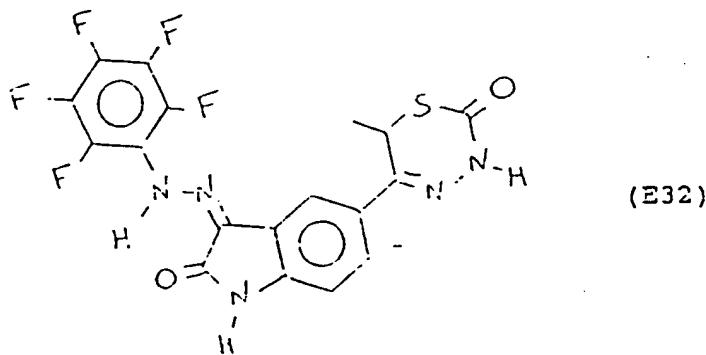
m.p. : 304°C

IR (KBr) : ν = 3,200; 1,700; 1,610; 1,470, 1,160; 1,115 cm⁻¹.

NMR (DMSO-d₆) : δ = 1.51 (d, J = 7.1Hz, 3H, CH₃CH); 4.83 (q, J = 7.1Hz, 1H, CH₃CH); 7.0-8.1 (m, 7H, including 4H phenyl ring and 3H Ar); 11.42 (s, 1H, exch. D₂O, NH); 11.68 (s, 1H, exch. D₂O, NH); 13.28 (s, 1H, exch. D₂O, NH).

Example 32

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(pentafluorophenylhydrazone)



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and pentafluorophenyl hydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 92%

m.p. : 285°C

IR (KBr) : ν = 3,250; 1,700; 1,620; 1,600, 1,545; 1,525 cm⁻¹.

NMR (DMSO-d₆) : δ = 1.47 (d, J = 7.1Hz, 3H, CH₃CH); 4.78 (q, J = 7.1Hz, 1H, CH₃CH); 7.02 (d, J = 8.3Hz, 1H, Ar); 7.77 (d, J = 8.3Hz, 1H, Ar); 7.88 (s, 1H, Ar); 11.47 (s, 1H, exch. D₂O, NH); 11.65 (s, 1H, exch. D₂O, NH); 12.51 (s, 1H, exch. D₂O, NH).

Example 33

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-(methylsulfonyl)phenyl hydrazone] monoacetonitrile complex

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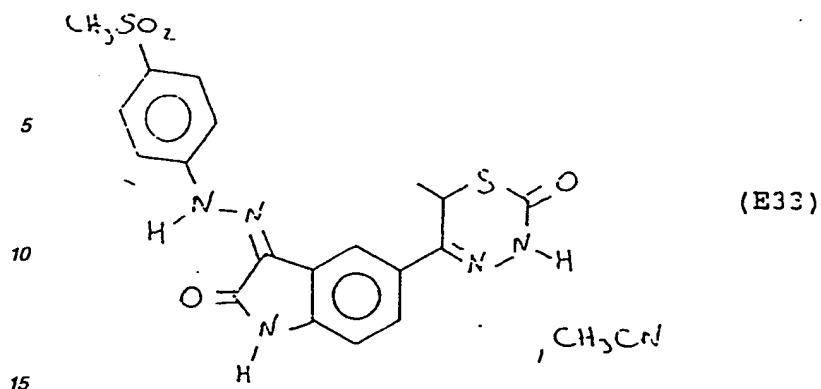
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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 4 methylsulfonylphenylhydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 90%

m.p. : 232°C

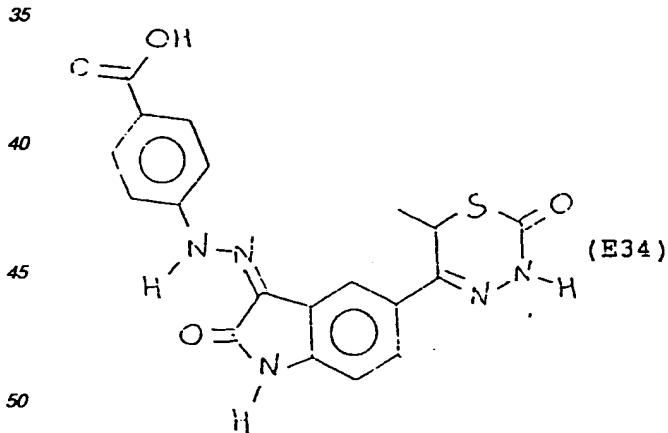
This desired compound was crystallised as a complex with 1 equivalent of acetonitrile.

IR (KBr) : $\nu = 3,250; 2,250$ (CH₃CN); 1,690, 1,620; 1,600; 1,560; 1,140 cm⁻¹.

25 NMR (DMSO-d₆): δ = 1.50 (d,J=7.1Hz,1H,CH₃CH); 2.08 (s,3H,CH₃CN); 3.21 (s,3H,CH₃SO₂); 4.83 (q,J=7.1Hz,CH₃CH); 7.02 (d,J=8.3Hz,1H,Ar); 7.69 (d,J=8.8Hz,2H,phenyl); 7.78 (dd,J=8.3Hz,J'=1.6Hz,1H,Ar); 7.90 (d,J=8.8Hz,2H,phenyl); 8.05 (d,J'=1.6Hz,1H,Ar); 11.38 (s,1H,exch.D₂O,NH); 11.70 (s,1H,exch.D₂O,NH); 12.81 (s,1H,exch.D₂O,NH).

30 Example 34

4-[2-[5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)2,3-dihydro-2-oxo-1H-indol-3-ylidenehydrazino]benzoic acid



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 4 hydrazinobenzoic acid and following the method described in Example 21, the desired compound was obtained.

Yield : 95%

m.p. : > 320°C

IR (KBr) : $\nu =$

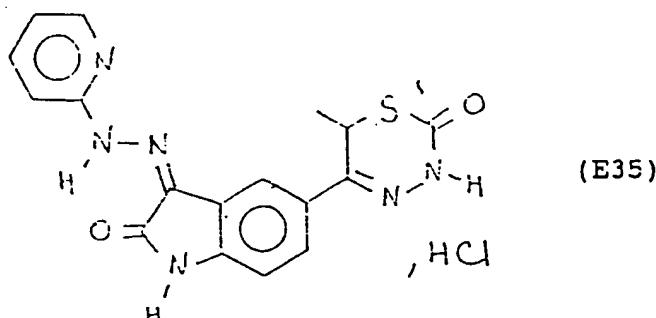
NMR (DMSO- d_6): $\delta = 1.50$ (d, $J = 7.1$ Hz, 1H, CH_3CH); 4.85 (q, $J = 7.1$ Hz, 1H, CH_2CH_3).

11.70 (s,1H,exch.D₂O,NH); -7.03 (s, δ =-7.1Hz,1H,CH₂Cl₂); 4.65 (q, J =7.1Hz,1H,CH₂Cl₂); 7.02 (d, J =8.3Hz,1H,Ar); 7.56 (d,AB, J =8.7Hz,2H,phenyl); 7.77 (dd,J=8.3Hz,J'=1.7Hz,1H,Ar); 7.95 (d,AB,J=8.7Hz,2H,phenyl); 8.03 (d,J'=1.7Hz,1H,Ar); 11.35 (s,1H,exch.D₂O,NH); 11.67 (s,1H,exch.D₂O,NH); 12-13 (m,1H, xch.D₂O,COOH); 12.80 (s,1H,exch.D₂O,NH).

Example 35

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(2-pyridylhydrazone) monohydrochloride

5



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 2-pyridylhydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 31%

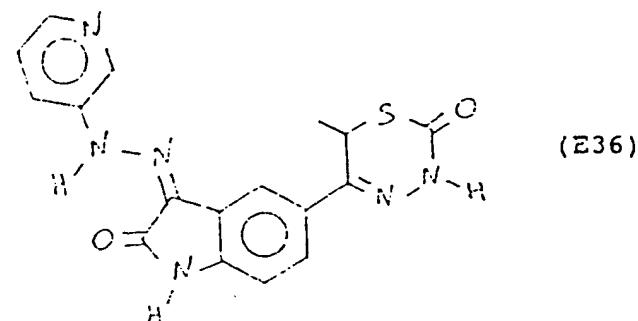
m.p. : 288°C

IR (KBr) : $\nu = 1,680; 1,630; 1,530 \text{ cm}^{-1}$.
NMR (DMSO- d_6) : $\delta = 1.49$ (d, $J = 6.9\text{Hz}$, 3H, CH_3CH); 4.84 (q, $J = 6.9\text{Hz}$, 1H, CH_3CH); 7.08 (d, $J = 8.2\text{Hz}$, 1H, Ar); 7.77-8.00 (m, 3H, pyridine); 8.42 (d, $J = 8.0\text{Hz}$, 1H, Ar); 8.93 (m, 1H, pyridine); 9.15 (s, 1H, Ar); 11.71 (s, 2H, exch. $\text{D}_2\text{O}, \text{NH}$); 13.79 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$).

Example 36

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(3-pyridylhydrazone)

35



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and 3-pyridylhydrazine and following the method described in Example 21, the desired compound was obtained.

Yield : 64%

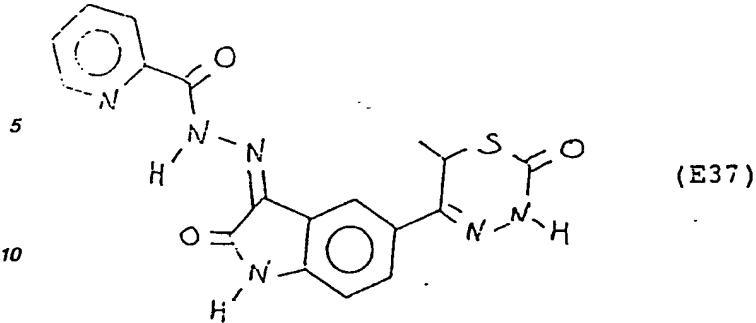
m.p. : 275°C

IR (KBr) : $\nu = 1,700; 1,620; 1,600; 1,570 \text{ cm}^{-1}$.
NMR (DMSO- d_6) : $\delta = 1.50$ (d, $J = 7.1\text{Hz}$, 3H, CH_3CH); 4.84 (q, $J = 7.1\text{Hz}$, 1H, CH_3CH); 7.01 (d, $J = 8.3\text{Hz}$, 1H, Ar); 7.37-7.44 (m, 1H, Py); 7.77 (d, $J = 8.3\text{Hz}$, 1H, Ar); 7.90-7.95 (m, 1H, Py); 8.03 (s, 1H, Ar); 8.27 (m, 1H, Py); 8.79 (m, 1H, Py); 11.31 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 11.68 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 12.63 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$).

Example 37

2-Pyridinecarboxylic acid,
2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide

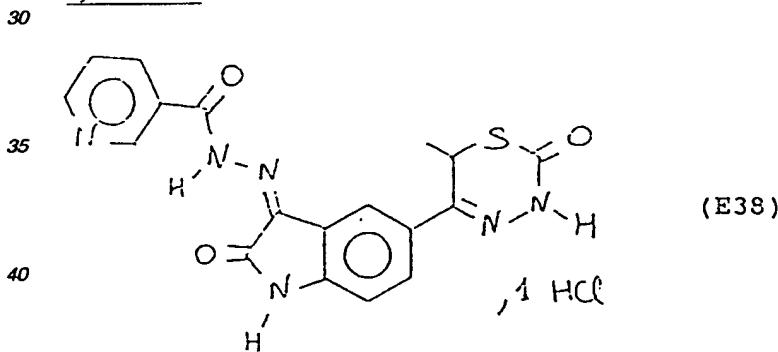
65



15 Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and picolyl hydrazide and following the method described in Example 21, the desired compound was obtained.
Yield : 26%
m.p. : >300°C
20 IR (KBr) : ν = 1,740; 1,620; 1,500 cm^{-1} .
NMR (DMSO-d₆) : δ = 1.58 (d, J=7.1Hz, 3H, CH₃CH); 4.77 (q, J=7.1Hz, 1H, CH₃CH); 7.04 (d, J=8.3Hz, 1H, Ar); 7.7-7.9 (m, 2H, Ar, pyridine); 8.1-8.3 (m, 2H, Ar, pyridine); 8.50 (s, 1H, Ar); 8.92-8.95 (m, 1H, Ar); 11.17 (s, 1H, exch. D₂O, NH); 11.88 (s, 1H, exch. D₂O, NH); 12.31 (s, 1H, exch. D₂O, NH).

25 Example 38

3-Pyridinecarboxylic acid,
2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide
hydrochloride



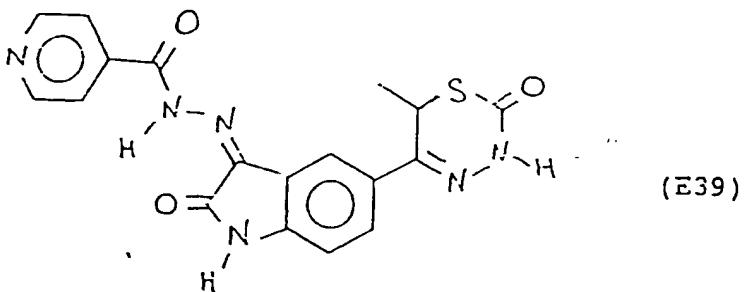
45 Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and nicotinic acid hydrazide and following the method described in Example 21, the desired compound was obtained.
Yield : 36%
50 m.p. : >300°C
IR (KBr) : ν = 1,700; 1,640; 1,620; 1,665; 1,505; 1,440 cm^{-1} .
NMR (DMSO-d₆) : δ = 1.51 (d, J=5.7Hz, 3H, CH₃CH); 4.81 (q, J=5.7Hz, 1H, CH₃CH); 6.9-8.4 (m, 7H, Ar + pyridine); 11.34 (m, 1H, exch. D₂O, NH); 11.67 (m, 1H, exch. D₂O, NH); 12.76 (m, 1H, exch. D₂O, NH).

55 Example 39

4-Pyridinecarboxylic acid,
2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide

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Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and isonicotinic acid hydrazide and following the method described in Example 21, the desired compound was obtained.

Yield : 68%

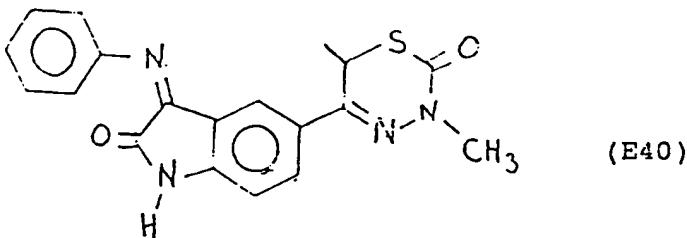
m.p. : 307°C

IR (KBr) : $\nu = 1,700; 1,610; 1,280 \text{ cm}^{-1}$.

NMR (DMSO-d₆) : $\delta = 1.49$ (d, $J = 7.0 \text{ Hz}$, 3H, CH₃CH); 4.87 (q, $J = 7 \text{ Hz}$, 1H, CH₃CH); 7.06 (d, $J = 8.4 \text{ Hz}$, 1H, Ar); 7.80 (d, $J = 5.8 \text{ Hz}$, 2H, pyridine); 7.91 (d, $J = 8.4 \text{ Hz}$, 1H, Ar); 8.00 (s, 1H, Ar); 8.88 (d, $J = 5.8 \text{ Hz}$, 2H, pyridine); 11.72 (s, 1H, exch. D₂O, NH); 12-15 (m, 2H, exch. D₂O, 2xNH).

Example 40

1,3-Dihydro-5-(3,6-dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one



4g (11.4 mmoles) 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, were dissolved in 35ml DMF dried over molecular sieves.

1g (23 mmoles) 60% sodium hydride were added portionwise, then 1.62g (11.4 mmoles) methyl iodide were added dropwise. The mixture was stirred overnight at room temperature. 100ml water were added and the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and purified by column chromatography (silica, eluent : methanol 1% in chloroform).

Yield : 29%

m.p. : 253°C

IR (KBr) : $\nu = 3,200; 1,745; 1,615; 1,300 \text{ cm}^{-1}$.

NMR (DMSO-d₆) : $\delta = 1.29$ (d, $J = 7.0 \text{ Hz}$, 3H, CH₃CH); 3.28 (s, 3H, NCH₃); 4.32 (q, $J = 7.0 \text{ Hz}$, 1H, CH₃CH); 6.9-8.1 (m, 8H including 5H phenylring and 3H Ar); 11.20 (m, 1H, exch. D₂O, NH)

A minor isomer (25%) gives supplementary peaks at 1.49 ppm (d, $J = 7.0 \text{ Hz}$, CH₃CH); 3.45 (s, NCH₃); and 4.85 (q, $J = 7.0 \text{ Hz}$, CH₃CH).

Example 41

5-(3,6-Dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(phenylhydrazone)

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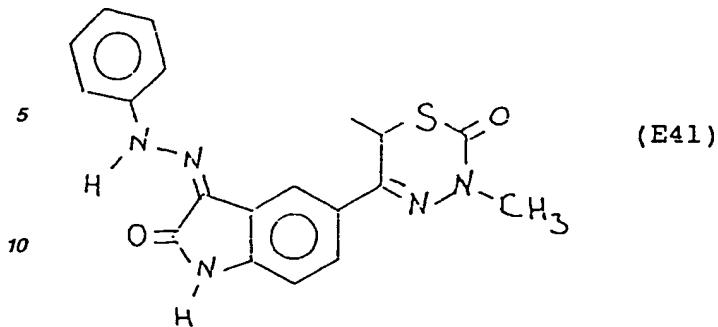
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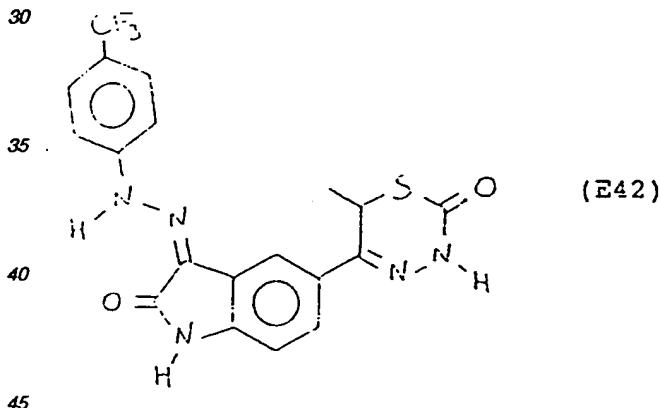
65



15 Starting from 1,3-dihydro-5-(3,6-dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one, and phenyl hydrazine and following the method described in Example 21, the desired compound was obtained.
Yield : 83%
m.p. : 268°C

20 IR KBr : $\nu = 3,150; 1,690; 1,615; 1,555; 1,240; 1,160 \text{ cm}^{-1}$.
NMR (DMSO- d_6) : $\delta = 1.51$ (d, $J=7.0\text{Hz}$, 3H, CH_3CH); 3.47 (s, 3H, NCH_3); 4.85 (q, $J=7.0\text{Hz}$, 1H, CH_3CH); 7.0-8.1 (m, 8H including 5H, phenylring and 3H, Ar); 11.31 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$); 12.76 (s, 1H, exch. $\text{D}_2\text{O}, \text{NH}$).

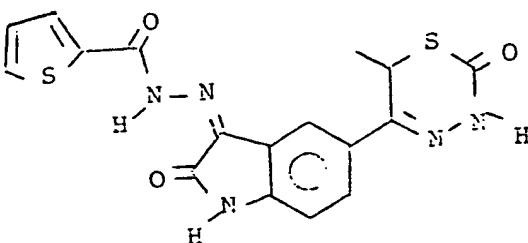
25 Example 42
5 (3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H indole-2,3-dione
3-[4-trifluoromethylphenylhydrazone]



50 1g (6.2mmoles) 4-aminobenzotrifluoride, in 16ml water containing 7ml hydrochloric acid were diazotized at 0-5°C with a cold solution of 430mg (6.3mmoles) sodium nitrite in 8ml water. This solution was added dropwise to a solution of 1.62g (6.2mmoles) 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one in 20ml ethanol and 25ml DMF. After 1 hour stirring at 0-5°C, the precipitate was filtered off, washed with methylene chloride, and hot methanol and dried under vacuum.

Yield : 51%
m.p. : > 300°C
IR (KBr) : $\nu = 1,705; 1,615; 1,570; 1,330 \text{ cm}^{-1}$.
NMR (DMSO- d_6) : mixture Z + E : $\delta = 1.52$ (2d, 3H, CH_3CH); 4.83 (m, 1H, CH_3CH); 6.9-8.5 (m, 7H including 4H phenylring and 3H Ar); 10.9-12.8 (m, 3H, exch. $\text{D}_2\text{O}, \text{NH}$).

60 Example 43
2-Thiophenecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide



Starting from 1,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one and 2-thiophene carboxylic acid hydrazide and following the method described in Example 21, the desired compound was obtained.

Yield: 35%

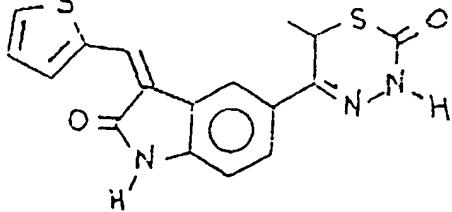
m.p.: >300°C

IR: (KBr): $\nu = 3.400, 1.650, 1.615, 1.280, 1.170, 1.110 \text{ cm}^{-1}$

NMR: (DMSO- d_6) $\delta = 1.50$ (d, $J=7.1\text{Hz}$, 0.9H, CH_3CH , isomer A); 1.60 (d, $J=7.0\text{Hz}$, 2.1H, CH_3CH , isomer B); 4.6–4.8 (m, 1H, CH_3CH , isomers A+B); 6.9–8.1 (m, 6H, thiophene H + Ar H); 8.7 (s, 1H, exch. D_2O , NH); 10.4–11.5 (m, 1H, exch. D_2O , NH); 11.7 (m, 1H, exch. D_2O , NH).

Example 44

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-thienylmethylen)-2H-indole-2-one



Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one and 2-thiophene carboxaldehyde and following the method described in Example 10, the desired compound was obtained.

Yield: 19%

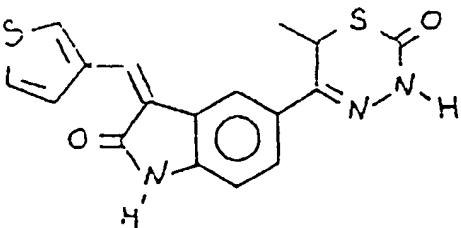
m.p.: 287°C

IR: (KBr): $\nu = 3.400, 1.695, 1.652, 1.625, 1.605, 1.200 \text{ cm}^{-1}$

NMR: (DMSO- d_6) $\delta = 1.46$ (d, $J=6.4\text{Hz}$, 0.5H, CH_3CH , isomer A); 1.54 (d, $J=7.0\text{Hz}$, 2.5H, CH_3CH , isomer B); 4.6–4.8 (m, 1H, CH_3CH , isomers A+B); 6.9–8.3 (m, 7H, 3 indol H, 3 thiophene H and 1 vinyl H); 10.62 (m, 0.15H exch. D_2O , NH, isomer A); 10.88 (m, 0.85H, exch. D_2O , NH, isomer B); 11.59 (m, 0.15H, exch. D_2O , NH, isomer A); 11.65 (m, 0.85H, exch. D_2O , NH, isomer B).

Example 45

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(3-thienylmethylen)-2H-indol-2-one



Starting from 5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,3-dihydro-2H-indol-2-one and 3-thiophene carboxaldehyde and following the method described in Example 10, the desired compound was obtained.

3-thiophene carboxaldehyde and following the method described in Example 10, the desired compound was obtained.

Yield: 53%

m.p.: > 300°C.

5 IR: (KBr): $\nu = 3.500, 1.690, 1.650, 1.630, 1.612, 1.210 \text{ cm}^{-1}$.
 NMR: (DMSO-d₆) $\delta = 1.53$ (d, J=7.1Hz, 3H, CH₃ CH); 4.7-4.8 (m, 1H, CH₃CH); 6.8-8.9 (m, 7H, 3 thiophene H, 1 vinyl H, 3Ar H); 10.88 (s, 1H, exch. D₂O, NH); 11.63 (s, 1H, exch. D₂O, NH).

Pharmacological Data

10

1. Measurement of myofibrillar Ca++-dependent Mg++-ATPase activity

The effect on myofibrillar Ca++ sensitivity and on maximal activity of myofibrillar Ca++-dependent Mg++-ATPase was determined on canine cardiac myofibrils.

15

(a) Contractile protein preparation

Cardiac myofibrils free of membrane contaminants were prepared from left ventricular tissue of dog hearts using a modification of the method described by SOLARO et al, Biochem. Biophys. Acta, 245, 259-262, (1971). Before centrifugation, the heart homogenate was filtered through gauze.

20

After Triton X-100 treatments, the myofibrillar fraction was washed once by resuspension and centrifugation in 10 volumes of 1 mM EGTA, 60ml KC1, 30 mM imidazole, 2 mM MgCl₂, pH 7.0. The pellet was then washed three times in 10 volumes of the same buffer without EGTA. Before the last centrifugation, the suspension of myofibrils was filtered through a stainless steel sieve with 0.25 mm meshes.

25

Myofibrils were kept in pellet overnight. Before use, the pellet was suspended in a small amount of buffer, the protein concentration was determined by the method of BRADFORD M., Anal. Biochem., 1976, 72, 248 and adjusted in order to have a concentration between 6 and 7mg/ml.

(b) Myofibrillar ATPase activity

30

Ca++-dependent myofibrillar ATPase activity was determined at 21°C, pH 7.0, by measuring the rate of release of inorganic phosphate. All assays were performed within 24hrs. of final purification, using the method described by SOLARO and RUEGG, CIRC. RES., 51, 290-4, (1982). Reaction mixtures (4ml) containing 0.6 - 0.7 mg/ml myofibrillar protein, 80mM KC1, 20 mM imidazole, 3 mM MgCl₂, 1 mM EGTA, the desired amount of CaCl₂, and the indicated concentration of drug or appropriate vehicle were preincubated for 6 min. prior to assay. The amount of CaCl₂ was varied between 0 and 0.9 mM and the pCa (-log free Ca++) computed using $2.514 \times 10^6 \text{ M}^{-1}$ as the apparent affinity of Ca++ for EGTA at pH 7.0.

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Reactions were initiated by the addition of Na₂ATP to final concentration of 2 mM After an incubation period of 12 min., reactions were quenched- by the addition of an equal volume of ice-cold 10% trichloroacetic acid. The protein was pelleted by centrifugation (2000g, 15 min.) and Pi was assayed in the supernatant fraction using a modification of the method described by LANZETTA et al, Anal. Biochem., 100, 95-97, (1979).

40

The following solutions were prepared:

(1) 3.7% ammonium heptamolybdate in 0.12 N H₂SO₄

(2) 0.074% malachite green oxalate in 1% polyvinylic alcohol.

45

The colour reagent was prepared by mixing an equal volume of solution (1) and (2) 15 min. before the assay. For the assay, 1700 μl of 1% H₂SO₄ and 1 ml of colour reagent were added to 100 μl of sample. Colour development occurred at room temperature for 30 min. and was quenched by the addition of 200 μl of 1 M tri-potassium citrate. The absorbance was measured at 620 millimicrons.

50

The effect of each compound, tested at the indicated concentration, on the relation between pCa and percent activation was determined taking 100% for the maximum ATPase activity obtained with vehicle alone. The effect on Ca++ sensitivity was quantified by measuring the shift of the pCa giving 50% of the maximal control ATPase activity.

55

The effect on maximal ATPase activity was expressed as the percent change of ATPase activity for pCa = 5.47. Mean effects on myofibrillar ATPase activity were obtained from 1 to 5 preparations, (compounds tested at $2 \times 10^{-4}\text{M}$).

60

65

Results

Example No	CANINE CARDIAC PDE		CANINE MYOFIBRIL ATPase	
	CAM IC ₅₀ (μM)	CGI IC ₅₀ (μM)	10 μM pCa/ max	30 μM pCa/ max
1	7.9 (n=3)	0.66 (n=3)	0.19 ± 0.09 +5 ± 0	0.25 ± 0.07 +1 ± 2
2	6.9 (n=3)	1.3 (n=4)	0.24 ± 0.01 +5 ± 2	0.60 ± 0.11 +13 ± 4
3	>300 (n=3)	0.27 (n=3)	—	+0.33 ± 0.05 +3 ± 3
4	>300 (n=3)	0.44 (n=3)	—	—
5	>>300 (n=3)	0.13 (n=6)	—	—
6	>>300 (n=3)	1.2 (n=3)	—	+0.38 ± 0.06 -2 ± 6
7	42.0 (n=3)	2.3 (n=3)	—	+0.17 ± 0.02 -3 ± 5
8	19.0 (n=3)	1.20 (n=3)	—	+0.87 ± 0.01 2 ± 3
9	31.0 (n=3)	2.10 (n=3)	—	+0.05 ± 0.07 -20 ± 3
10	20.0 (n=3)	0.35 (n=3)	—	+0.43 ± 0.07 -13 ± 3
11	>>300 (n=2)	0.68 (n=3)	—	+0.36 ± 0.05 8 ± 2
12	—	1.80 (n=3)	—	+0.08 ± 0.02 -1 ± 2
13	—	14.0 (n=3)	—	+0.07 ± 0.02 2 ± 2
14	5.6 (n=3)	0.62 (n=3)	—	+0.12 ± 0.02 0 ± 3
15	—	—	—	+0.08 ± 0.04 2 ± 4

Results

Example No	CANINE CARDIAC PDE		CANINE MYOFIBRIL ATPase	
	CAM IC ₅₀ (μM)	CGI IC ₅₀ (μM)	10 μM pCa/ max	30 μM pCa/ max
16	—	—	—	+0.17 ± 0.03 1 ± 4
17	23.0 (n=3)	0.43 (n=3)	—	+0.60 ± 0.07 -16 ± 3
18	4.0 (n=3)	1.90 (n=3)	—	+0.04 ± 0.08 -28 ± 4
19	—	—	—	+0.23 ± 0.06 -14 ± 7
20	—	—	—	+0.19 ± 0.08 -13 ± 5
21	—	—	1.07 ± 0.02 41 ± 2	+1.30 ± 0.00 -42 ± 7
22	—	—	—	+0.64 ± 0.1 21 ± 4
23	—	—	—	+0.05 ± 0.02 8 ± 6
24	—	—	—	+0.49 ± 0.06 -2 ± 5
25	—	—	—	+0.49 ± 0.06 22 ± 3
26	—	—	—	+0.65 ± 0.05 17 ± 2
27	—	—	—	+0.05 ± 0.03 -1 ± 0
28	—	—	—	+0.94 ± 0.05 20 ± 5
29	—	—	—	+0.76 ± 0.1 25 ± 4
30	—	—	—	+1.01 ± 0.07 28 ± 6

Results

Example No	CANINE CARDIAC PDE		CANINE MYOFIBRIL ATPase	
	CAM IC ₅₀ (μM)	CGI IC ₅₀ (μM)	10 μM pCa/ max	30 μM pCa/ max
31	—	—	—	+0.43 ± 0.04 26 ± 7
32	—	—	—	+0.10 ± 0.04 -1 ± 7
33	—	—	—	+0.37 ± 0.05 3 ± 1
34	—	—	—	+0.40 ± 0.02 5 ± 2
35	—	—	—	+0.05 ± 0.05 0 ± 1
36	—	—	—	+0.92 ± 0.06 24 ± 5
37	—	—	—	+0.14 ± 0.03 -9 ± 1
38	—	—	1.10 ± 0.02 34 ± 7	+1.05 ± 0.06 34 ± 5
39	—	—	—	+0.04 ± 0.02 3 ± 2
41	—	—	—	+0.11 ± 0.04 7 ± 2
42	—	—	—	+0.30 ± 0.02 11 ± 4

2. Cardiotonic activity in the conscious instrumented Dog

Male Beagle dogs, at least 2 years old, weighing 12 to 18 kg were anaesthetised with pentobarbital sodium (30 mg/kg i.v.). Respiration was maintained by a Harvard pump, model 613a. The heart was exposed through a left thoracotomy and a pericardial cradle was formed. A high fidelity micromanometer (Koenigsberg P5-P7) was inserted into left ventricular lumen through a stab incision at the apex. Wires were exteriorised to the back of the animals, placed into a size adapted jacket, and the chest closed. The experiments were conducted on the conscious dogs, 1 or 2 weeks after the surgery, when the animals had completely recovered.

Measured parameters were : first derivative of left ventricular pressure, (dP/dt, mmHg/sec); heart rate (HR, beats/min.). A control period recording of 90 min. was made with the dogs placed in a quiet room, the recordings being made outside. Compounds to be tested were administered orally in gelatin capsules and the parameters measured for 5 hrs. at least.

Results were expressed as the percentage of the maximum ± SEM.

Results

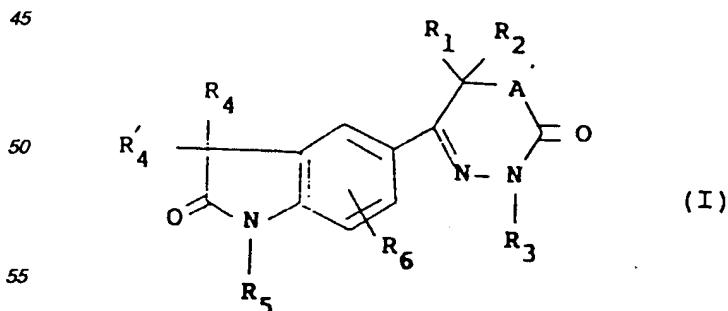
ANAESTHETISED DOG-I.V.						
	Example No.	Dose mg/kg	AoBP	H.R.	dP/dt Max	AoBF
10	1	0.1	+4	+13	+31	+8
		0.3	-9	+30	+54	+16
		1.0	-20	+55	123	+33
15	2	0.1	+ 4 ± 2	+13 ± 8	+31 ± 9	+8 ± 2
		0.3	- 9 ± 1	+26 ± 10	+54 ± 20	+16 ± 1
		1.0	-20 ± 5	+55 ± 21	+123 ± 56	+33 ± 5
20	3	0.1	-14 ± 7	+28 ± 6	+17 ± 6	-30 ± 12
		0.3	-29 ± 6	+54 ± 11	+70 ± 5	-63 ± 8
		1.0	-30 ± 1	+93 ± 7	+126 ± 9	-50 ± 12
25	5	0.1	-14 ± 6	+ 8 ± 1	+ 7 ± 2	-25 ± 1
		0.3	-12 ± 3	+18 ± 7	+24 ± 6	-34 ± 5
		1.0	-12 ± 1	+19 ± 16	+42 ± 16	-28 ± 4
		3.0	-19 ± 3	+58 ± 0	+116 ± 31	-37 ± 2
30	17	0.3	- 8 ± 2	+ 9 ± 3	+ 6 ± 2	+14 ± 2
		1.0	- 7 ± 1	+22 ± 5	+35 ± 8	+16 ± 1
		3.0	-20 ± 7	+52 ± 13	+81 ± 18	+18 ± 4
35	31	0.01	- 8 ± 1	+ 8 ± 2	+ 9 ± 3	+11 ± 5
		0.03	-15 ± 1	+30 ± 4	+44 ± 13	+19 ± 8
		0.1	-23 ± 2	+39 ± 6	+93 ± 13	+13 ± 6

40

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof,

45



in which,

R₁ is hydrogen or lower alkyl;R₂ is hydrogen or lower alkyl;

R₄ and R_{4'} together form a group =N-Ra, or =CRaRb, where Ra is hydrogen, lower alkyl, aryl, aryloxy, lower alkylcarbonyl, arylcarbonyl, aryloxycarbonyl, lower alkoxy, lower alkoxy carbonyl, lower alkoxy carbonyl alkoxy, lower -thioalkoxy, hydroxy, nitrile, heterocyclic, or -NRcRd, where Rc is hydrogen, lower alkyl, cycloalkyl, aryl, aralkyl, lower alkylcarbonyl, arylcarbonyl, aminocarbonyl, aminothiocarbonyl, aminoiminocarbonyl, lower alkoxy carbonyl, lower alkoxythiocarbonyl, aryloxycarbonyl, thiocarbonyl,

nitrile, carboxyl, heterocycl or h terocyclcarbonyl, and Rd is hydrogen or lower alkyl; Rb is hydrogen, lower alkyl, aryl, lower alkylcarbonyl, lower alkoxy carbonyl, nitrile or nitro;
or R₄ is -NH-Ra, in which Ra is as defined above, and R_{4'} is hydrogen or lower alkyl;
each of R₃ and R₅ is independently hydrogen, lower alkyl, aryl, lower alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclcarbonyl, optionally substituted aminocarbonyl, lower alkoxy carbonyl or aryloxycarbonyl;
R₆ is hydrogen, lower alkyl or halogen;
and A is sulphur, oxygen, -NH- or -CH₂-.

5

2. A compound according to claim 1 in which A is sulphur.

10

3. A compound according to claim 1 or 2 in which each of R₁, R₂, R₃, R₅ and R₆ is independently hydrogen or C₁₋₆ alkyl.

4. A compound according to any one of claims 1 to 3 in which 'aryl' represents phenyl optionally substituted by one or more atoms or moieties selected from amino, nitro, hydroxyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, trifluoromethyl, C₁₋₆ alkyl sulphonyl and carboxyl.

15

5. A compound according to any one of claims 1 to 3 in which 'heterocycl' represents pyridyl, thiényl or imidazolyl.

6. A compound selected from:

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-hydroxyimino-2H-indol-2-one;

20

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4 thiadiazin-5-yl)-3-methoxyimino-2H-indol-2-one;

O-Methyl 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazine carbothioate;

2-[2,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]-hydrazine carbothioamide;

25

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-phenylhydrazone;

1,3,6-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one;

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-hydrazone;

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylamino-2H-indol-2-one, hydrochloride;

[5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,2-dihydro-2-oxo-3H-indol-3-ylidene]-propane-dinitrile;

30

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylmethylene-2H-indol-2-one;

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenoxyimino-2H-indol-2-one;

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[2-(aminomethanimino)hydrazone];

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[2-(4,5-dihydro-1H-2-imidazolyl)hydrazone];

35

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(4-dimethylaminophenylimino)-2H-indol-2-one;

Methyl 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]-hydrazine carboxylate

40

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-nitrophenylmethylene)-2H-indol-2-one;

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-[(2-hydroxyphenyl)methylene]-2H-indol-2-one;

45

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(4-pyridylmethylene)-2H-indol-2-one;

1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(3-pyridylmethylene)-2H-indol-2-one;

50

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-methyl)phenylhydrazone];

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(phenylmethyl)hydrazone];

Ethyl[[[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]amino] oxy]acetate;

55

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-(1,1-dimethylethyl)phenylhydrazone];

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(cyclohexylhydrazone);

60

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(methylphenylhydrazone);

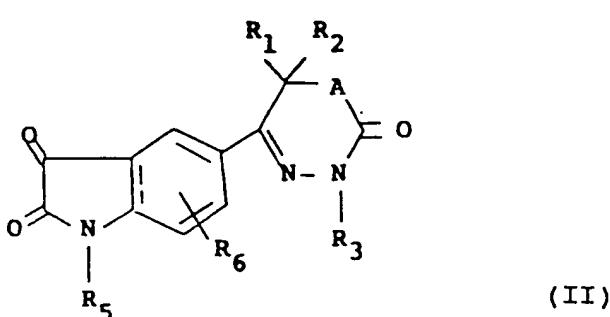
5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(3,4-dichlorophenyl)hydrazone];

5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-methoxy)phenylhydrazone];

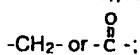
5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-chloro)phenylhydra-

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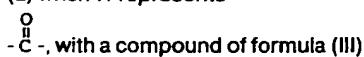
zone];
 5 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-fluoro)phenylhydrazone];
 5 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(2-trifluoromethyl)phenylhydrazone];
 10 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(pentfluorophenylhydrazone);
 10 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-(methylsulfonyl)phenylhydrazone] monoacetonitrile complex;
 15 4-[2-[5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)]2,3-dihydro-2-oxo-1H-indol-3-ylidene]hydrazino]benzoic acid;
 15 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(2-pyridylhydrazone) monohydrochloride;
 20 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(3-pyridylhydrazone);
 20 2-Pyridinecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide;
 25 3-Pyridinecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide hydrochloride;
 25 4-Pyridinecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide;
 30 1,3-Dihydro-5-(3,6-dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one;
 30 5-(3,6-Dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(phenylhydrazone);
 30 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-trifluoromethylphenylhydrazone];
 35 2-Thiophenecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide;
 40 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-thienylmethylen)-2H-indol-2-one;
 40 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(3-thienylmethylen)-2H-indol-2-one.
 45 7. A process for preparing a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises treating a compound of formula (II)



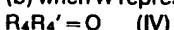
in which R₁, R₂, R₃, R₅, R₆ and A are as defined in formula (I) and W represents



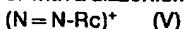
(a) when W represents



60 in which R₄R₄' represents >N-R_a , >CHR_a or $\text{>CR}_a\text{R}_b$ as defined in claim 1, or
 (b) when W represents $-\text{CH}_2-$, with a compound of formula (IV)



where R₄ and R₄' are = N-R_a or = CR_aR_b as defined in formula (I),
 or with a diazonium salt containing an anion of formula (V)



where R_c is as defined in formula (I),
and thereafter if desired converting a compound of formula (I) thereby produced to a pharmaceutically acceptable salt thereof or to a further compound of formula (I).

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5

9. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance.

10. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of heart disease.

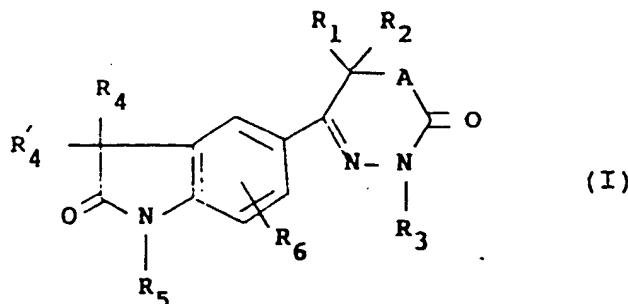
10

11. The use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of heart disease.

Claims for the following Contracting State: ES

1. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15



in which,

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R_1 is hydrogen or lower alkyl;

35

R_2 is hydrogen or lower alkyl;

R_4 and R_4' together form a group $=N-R_a$, or $=CR_aR_b$, where R_a is hydrogen, lower alkyl, aryl, aryloxy, lower alkylcarbonyl, arylcarbonyl, aryloxycarbonyl, lower alkoxy, lower alkoxy carbonyl, lower alkoxy carbonyl alkoxy, lower-thioalkoxy, hydroxy, nitrile, heterocycl, or $-NR_cR_d$, where R_c is hydrogen, lower alkyl, cycloalkyl, aryl, aralkyl, lower alkylcarbonyl, arylcarbonyl, aminocarbonyl, aminothiocarbonyl, aminoiminocarbonyl, lower alkoxy carbonyl, lower alkoxythiocarbonyl, aryloxycarbonyl, thiocarbonyl, nitrile, carboxyl, heterocycl or heterocyclic carbonyl, and R_d is hydrogen or lower alkyl; R_b is hydrogen, lower alkyl, aryl, lower alkylcarbonyl, lower alkoxy carbonyl, nitrile or nitro;

40

or R_4 is $-NH-R_a$, in which R_a is as defined above, and

R_4' is hydrogen or lower alkyl;

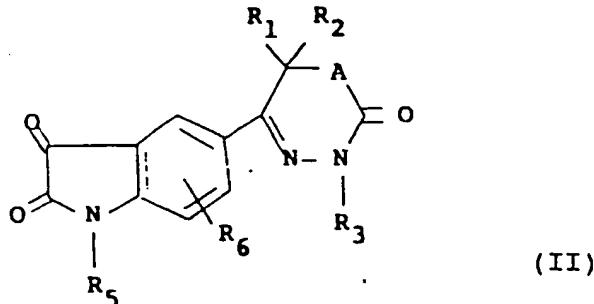
each of R_3 and R_5 is independently hydrogen, lower alkyl, aryl, lower alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heterocyclic carbonyl, optionally substituted aminocarbonyl, lower alkoxy carbonyl or aryloxycarbonyl;

45

R_6 is hydrogen, lower alkyl or halogen;

and A is sulphur, oxygen, $-NH-$ or $-CH_2-$,

which comprises treating a compound of formula (II)



in which R_1 , R_2 , R_3 , R_5 , R_6 and A are as defined in formula (I) and W represents

50

$-CH_2-$ or $-C(=O)-$;

55

(a) when W represents

60

65

$\text{-C}=\text{O}$, with a compound of formula (III)



10 in which R₄R_{4'} represents >N-R_a, >CHR_a or >CR_aR_b as defined in claim 1, or
 (b) when when W represents -CH₂- with a compound of formula (IV)
 R₄R_{4'} = O (IV)
 where R₄ and R_{4'} are = N-Ra or = CR_aR_b as defined in formula (I),
 or with a diazonium salt containing an anion of formula (V)
 (N = N-Rc)⁺ (V)
 where Rc is as defined in formula (I),
 and thereafter if desired converting a compound of formula (I) thereby produced to a pharmaceutically acceptable salt thereof or to a further compound of formula (I).
 15 2. A process according to claim 1 in which A is sulphur.
 3. A process according to claim 1 or 2 in which each of R₁, R₂, R₃, R₅ and R₆ is independently hydrogen or C₁-6 alkyl.
 4. A process according to any one of claims 1 to 3 in which 'aryl' represents phenyl optionally substituted by one or more atoms or moieties selected from amino, nitro, hydroxyl, C₁-6 alkyl, C₁-6 alkoxy, halogen, trifluoromethyl, C₁-6 alkyl sulphonyl and carboxyl.
 20 5. A process according to any one of claims 1 to 3 in which 'heterocycl' represents pyridyl, thienyl or imidazolyl.
 6. A process according to claim 1 in which the compound of formula (I) is selected from:
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-hydroxyimino-2H-indol-2-one;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-methoxyimino-2H-indol-2-one;
 30 O-Methyl 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazine carbothioate;
 2-[2,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]-hydrazine carbothioamide;
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-phenylhydrazone;
 35 1,3,6-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one;
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-hydrazone;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylamino-2H-indol-2-one, hydrochloride;
 40 [5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1,2-dihydro-2-oxo-3H-indol-3-ylidene]-propane dinitrile;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylmethylen-2H-indol-2-one;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenoxyimino-2H-indol-2-one;
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[2-(aminomethanimino)hydrazone];
 45 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[2-(4,5-dihydro-1H-2-imidazolyl)hydrazone];
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(4-dimethylaminophenylimino)-2H-indol-2-one;
 50 Methyl 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazine carboxylate
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-nitrophenylmethylene)-2H-indol-2-one;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-[(2-hydroxyphenyl)methylene]-2H-indol-2-one;
 55 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(4-pyridylmethylene)-2H-indol-2-one;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(3-pyridylmethylene)-2H-indol-2-one;
 60 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-pyridylmethylene)-2H-indol-2-one;
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-methyl)phenylhydrazone];
 65 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(phenylmethyl)hydrazone];
 Ethyl[[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]

ne]amino] oxy]acetat ;
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-(1,1-dimethylethyl)phenylhydrazone];
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(cyclohexylhydrazone);
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(methylphenylhydrazone);
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(3,4-dichlorophenyl)hydrazone];
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-methoxy)phenylhydrazone];
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-chloro)phenylhydrazone];
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(4-fluoro)phenylhydrazone];
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[(2-trifluoromethyl)phenylhydrazone];
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(pentafluorophenylhydrazone);
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-(methylsulfonyl)phenylhydrazone] monoacetonitrile complex;
 4-[2-[5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)2,3-dihydro-2-oxo-1H-indol-3-ylidene]hydrazino]benzoic acid; 20
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(2-pyridylhydrazone) monohydrochloride;
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(3-pyridylhydrazone);
 2-Pyridinecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide; 25
 3-Pyridinecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide hydrochloride;
 4-Pyridinecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide; 30
 1,3-Dihydro-5-(3,6-dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-phenylimino-2H-indol-2-one;
 5-(3,6-Dihydro-3,6-dimethyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-(phenylhydrazone);
 5-(3,6-Dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-1H-indole-2,3-dione 3-[4-trifluoromethylphenylhydrazone];
 2-Thiophenecarboxylic acid, 2-[2,3-dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-2-oxo-1H-indol-3-ylidene]hydrazide; 35
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(2-thienylmethylen)-2H-indole-2-one;
 1,3-Dihydro-5-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)-3-(3-thienylmethylen)-2H-indole-2-one. 40
 7. A process for preparing a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 6, and a pharmaceutically acceptable carrier, which comprises admixing the compound and carrier preferably at 0°C to 100°C and 0.1 to 10 atmospheres pressure, such that the composition preferably contains from 1 to 1000mg of the compound per unit dose. 45
 8. The use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of heart disease.

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